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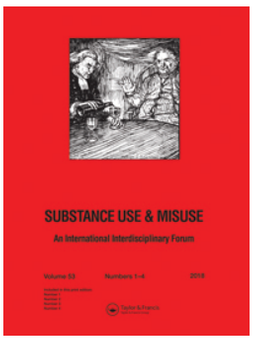

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ORIGINAL ARTICLE

A Systematic, Intensive Statistical Investigation of Data from the Comprehensive Analysis of Reported Drugs (CARD) for Compliance and Illicit Opioid Abstinence in Substance Addiction Treatment with Buprenorphine/naloxone

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ABSTRACT

Background: Buprenorphine and naloxone (bup/nal), a combination partial mu receptor agonist and low-dose delta mu antagonist, is presently recommended and used to treat opioid-use disorder. However, a literature review revealed a paucity of research involving data from urine drug tests that looked at compliance and abstinence in one sample. *Method*: Statistical analysis of data from the Comprehensive Analysis of Reported Drugs (CARD) was used to assess compliance and abstinence during treatment in a large cohort of bup/nal patients attending chemical-dependency programs from eastern USA in 2010 and 2011. *Results*: Part 1: Bup/nal was present in 93.4% of first ($n = 1{,}282$; $p < .0001$) and 92.4% of last ($n = 1{,}268$; $p < .0001$) urine samples. Concomitantly, unreported illicit drugs were present in 47.7% ($n = 655$, $p = .0261$) of samples. Patients who were compliant to the bup/nal prescription were more likely than noncompliant patients to be abstinent during treatment ($p = .0012$; odds ratio = 1.69 with 95% confidence interval (1.210, 2.354). Part 2: An analysis of all samples collected in 2011 revealed a significant improvement in both compliance ($p < 2.2 \times 10^{-16}$) and abstinence ($p < 2.2 \times 10^{-16}$) during treatment. *Conclusion/Importance*: While significant use of illicit opioids during treatment with bup/nal is present, improvements in abstinence and high compliance during maintenance-assisted therapy programs may ameliorate fears of diversion in comprehensive programs. Expanded clinical datasets, the treatment modality, location, and year of sampling are important covariates, for further studies. The potential for long-term antireward effects from bup/nal use requires consideration in future investigations.

KEYWORDS
Abstinence; buprenorphine/naloxone; compliance; opioid maintenance therapy programs; substance-use disorder; urine drug screens

Introduction

Substance-seeking behaviors have negative and devastating consequences (Policy, 2004; Rehm et al., 2009). Opioid-use disorder is associated with many adverse, health and social consequences for society: infectious disease transmission, elevated healthcare costs, public disorder, crime and fatal overdose (Lynch et al., 2014). A combination of buprenorphine a partial mu-receptor agonist that blocks kappa opioid-type receptors, and naloxone a low-dose narcotic delta/mu-receptor antagonist, to prevent injection by inducing withdrawal (Chiang & Hawks, 2003; Wesson & Smith, 2010) is being used for opioid maintenance therapy programs. The Federal Drug Addiction Treatment Act 2000 allows physicians who meet certain qualifications to treat opioid-dependent patients with buprenorphine and naloxone (bup/nal)

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combination. Many clinical studies have established that bup/nal maintenance is as effective as methadone maintenance, in reducing illicit opioid use and retaining patients in medication-assisted treatment (MAT) programs (Jaffe & O'Keeffe, 2003; Volkow, Frieden, Hyde, & Cha, 2014).

In 2014, Mattick et al. used Cochrane Collaboration methodology to evaluate buprenorphine and methadone maintenance compared to placebo in 31 trials that included 5,430 participants. They found that when fixed medium or high doses are used, buprenorphine and methadone are equally effective for treatment retention in and suppression of illicit opioid use. Specifically, they found buprenorphine at dosages greater than 2 mg per day maintains treatment retention better than placebo. While at 16 mg or more per day, buprenorphine was found to reduce illicit substance use compared with placebo as monitored by urinalysis. However, buprenorphine retains fewer people compared to methadone, when doses are low and fixed or flexibly delivered (Mattick, Breen, Kimber, & Davoli, 2014).

Two hypotheses formed the basis of this retrospective post hoc study. They were that patients in programs being treated with bup/nal: (1) adhere to prescribed bup/nal treatment medications and (2) abstain from illicit drug use during treatment.

Previous studies have used biological markers to determine compliance to known dosages of treatment medications or measure nonabstinence during treatment (Balhara & Jain, 2012; Baros, Latham, Moak, Voronin, & Anton, 2007; Gerra, Fantoma, & Zaimovic, 2006; Kumari et al., 2016; McDermott et al., 2015; Moore et al., 2016; Pal Singh Balhara & Jain, 2012). Other studies have focused on meaningful comparisons regarding treatment modalities, efficacy methadone vs. bup/nal, and determination of risk factors for compliance and treatment success. Many of these studies have used short follow-up periods, and researchers have focused largely on retention rates, chart reviews, instances of buprenorphine administration, interviews, self-report of heroin use and criminal activity, and telephone or internet communication, to measure adherence and abstinence (Fareed et al., 2014; Maas, Barton, Maskrey, Pinto, & Holland, 2013; Mattick et al., 2014; Moore et al., 2016; Parran et al., 2010; Tkacz, Severt, Cacciola, & Ruetsch, 2012).

This study, however, presents a systematic analysis of a large sample of data from patient urine drug screens (UDS) from a variety of treatment programs in five states over 2 years. Compliance with prescribed medication and nonabstinence during bup/nal maintenance treatment were measured in a single sample of analytes (Blum et al., 2011; Blum et al., 2014; Hill et al., 2013).

The statistical analysis has two parts. Part 1 examines compliance and abstinence in first and last urine samples collected during treatment in 2010 and 2011 and explores outcomes across states, treatment modality and as a function of the level of care. Part 2 focuses on trends in compliance and abstinence over time.

Comprehensive analysis of reported drugs

The "Comprehensive Analysis of Reported Drugs" (CARD^{TM}) is a reporting system that uses laboratory results from validated urine drug testing profiles of prescription and illicit drugs.

The comprehensive drug-monitoring tools utilized in CARD^{TM} include 16 testing methodologies (standard enzyme immunoassay and liquid chromatography-tandem mass spectrometry measured by quantitative creatinine-adjusted immunoassay). These methods are employed to identify substances or metabolites from 28 distinct drug categories. With this process, 125 distinct drugs or metabolites can be determined. These methods have been developed to assist clinicians in managing patients with precision at intake, during treatment, and to determine individual and program outcomes (McCarberg, 2011). In summary, CARD^{TM} compares the self-report of illicit substance use and prescribed medication use, to the objective detection of drugs and medications measured by quantitative creatinine-adjusted immunoassay and molecular identification techniques.

The basis of the CARD^{TM} methodology is that when the test is ordered the drugs prescribed by the physician and the illicit drugs reported by the patient are noted. Drugs present in the body have been scientifically proven to exhibit specific conditional results on drug tests. The CARD^{TM} correlation process determines specific conditional drug tests results, reports on whether or not the drugs identified in the test are "expected" or "not expected" and assigns a written comment. The results are provided to the physician for each reported drug-to-analyte pair depending on the conditions established in the laboratory order; the self- and physician-reported drugs are "expected." Physicians are sent "alerts" regarding "not expected" test results in the report. Nearly 2,000 pharmacists' notes and associated conditions have been defined and can be analyzed automatically. All expected Food and Drug Administration (FDA) approved drugs for Substance Use Disorder (SUD) treatment and patient-reported substances are included in each UDS. Due to comorbidity, the following drug classes: anabolic steroids, antidepressants, hallucinogens, inhalants, muscle relaxants, opioids, psychostimulants, psychotropic, sedatives, hypnotics, and depressants are also included in the screen.

Expected or not expected results guide treatment plans and measure outcomes. Because drugs are metabolized into other reportable substances, the possibility exists that test results can be open to misinterpretation.

Table 1. Sample distribution over treatment modality, level of care, and minimum days between the samples.

Modality	*n* (%)	Level of care	*n* (%)	Minimum days between the samples
In-patient (IN)	36 (2.6)	In-patient (IP)	14 (1.0)	21
		Residential facility (RES)	22 (1.6)	30
Out-patient (OUT)	1,336 (97.4)	Intensive out-patient (IOP)	287 (20.9)	15
		Out-patient (OP)	863 (62.9)	30
		Opioid treatment program (OTP)	186 (13.6)	30
Total	1,372 (100)		1,372 (100.0)	

Clinicians are given access to Pharm. D. consultants to assist them in result interpretation. The information is used in clinical interactions with the client.

This innovative monitoring tool can also aggregate data from each client, within a clinical practice, to establish the percentages of clients who are compliant with medications-prescribed doses during treatment. The analysis also detects unexpected illicit drug use (nonabstinence) in patients tested, relative to expected reported drug use and aggregates that data.

A detailed explanation of CARD™ methodology can be found in the "CARD Rule Sets" in Supporting information S1 in a previously published paper (Blum et al., 2014). The FDA approved MAT; bup/nal is the focus of this data analysis.

Method

This study reports the results of a statistical analysis of unidentifiable data from CARD™, privately held at Dominion Diagnostics, LLC, North Kingston, RI. The data were used to evaluate treatment adherence and nonabstinence in a large clinical cohort from some eastern states in the United States. The Dominion pharmacy staff did determine whether prescription medications present in the results were licit or illicit. Before being accessed for this statistical analysis as part of the CARD process, each entry was tagged as being prescribed, or other, examples are, prescribed benzodiazepines, stimulant medications to treat Attention Deficit Hyperactivity Disorder (ADHD) or other substances such as opioids prescribed for an operative procedure or comorbid conditions. The entire data set (raw data) was deidentified and then vetted independently by the statistician.

The ethics committee from Path Foundation NY waived Institutional Review Board (IRB) approval and the requirement of consent by individual patients for the use of this database for this research analysis on November 29th, 2012. The nonpublic, anonymized data can be provided to researchers with prior written approval by Dominion Diagnostics, LLC.

Subject population

This present study is a statistical analysis of a subset of the data from a large cohort of 10,570 patients (including nontreatment patients) collected from addiction-treatment centers across six eastern states in the United States from 2010 to 2011.

The subset used in this study is, of data from the initial large cohort, restricted to those patients taking bup/nal ($n = 1{,}372$) stratified by treatment modality and five different levels of care (Table 1) from five states (Table 2).

The first statistical analysis (Part 1) was of data from the first and last urine specimens 2010 and 2011. Although some patients yielded multiple urine samples, to ensure the uniformity of the collection scheme, only the first and last urine samples were considered. In Table 1, the minimum number of calendar days between specimens was taken into consideration, and some patients who had changed the level of care were excluded.

The second statistical analysis (Part 2) was to determine trends in compliance and abstinence rates over time. The focus was to analyze data from all urine samples collected during the year 2011 from each patient prescribed the bup/nal combination.

Summary of demographic statistics

Part 1

The distribution of patients across two modalities and five levels of care are presented in Table 1. Most of the sample (97.4%) consisted of the out-patients of which 13.6% were in opioid treatment programs. It was found that 11.1% of the patients ($n = 152$) had both the first and last urine specimens collected in 2010, while 46.7% ($n = 641$) had both specimens collected in 2011. The rest of 42.2% ($n = 579$) had the first urine specimen collected in 2010 and the last specimen collected in 2011. That resulted in a total of 1,372 patients with first and last urine samples, who were on at least one prescription medication including bup/nal ($n = 1{,}372$; total 2,744 specimens). Indeed

Table 2. Sample distribution over states.

State	Sample size	Percentage
Maryland (MD)	86	6.3%
Maine (ME)	347	25.3%
North Carolina (NC)	78	5.7%
Rhode Island (RI)	173	12.6%
Vermont (VT)	688	50.1%
Total	1,372	100.0%

82.3% of the patients ($n = 1{,}129$) were prescribed bup/nal alone. The distribution of the number of days between the first and last urine samples is heavily right-skewed with ranges from 15 to 717 days. The median is 189 days with the interquartile range of 252 days. The mean and standard deviation of the sample are 224.6 and 165.2 days, respectively.

Patient distribution across five eastern states in the United States is presented in Table 2. South Carolina had only one bup/nal patient observation and hence was excluded from the analysis. The sample size is mostly skewed toward Maine and Vermont (VT).

Part 2

Trends in compliance and abstinence rates in UDS obtained from individuals, up to the extreme of 94 times, were examined. The initial subset ($n = 1{,}379$) included a few patients excluded from the first analysis because they had changed their level of care during 2011. The final subset was ($n = 1{,}299$) after 80 patients who had only one urine specimen in 2011 were excluded. It is noteworthy that Dominion Diganostics, LLc does not endorse such a high rate of UDS.

Statistical analysis

Statistical analysis was conducted using the discrete contingency analyses, the two-level binomial logistic regression model, and the generalized linear mixed model (GLMM) in the R package version 2.15.0.

The definitions of the terms used in this analysis are as follows:

Compliance: patient compliance to prescribed treatment medications during in-patient or out-patient recovery program.

- Compliance both: bup/nal detected in *both in the first and last* urine samples tested.
- Compliance first: bup/nal detected *in the first* urine sample.
- Compliance last: bup/nal detected *in the last* urine sample.

Abstinence: patient abstinence from all nonprescribed licit or illicit psychoactive substances during treatment.

- Abstinence both: CARD^{TM} did *not* detect *any* analyte that was not attributed to a reported prescription *in the first and last* urine samples tested.
- Abstinence first: CARD^{TM} did *not* detect *any* analyte that was not attributed to a reported prescription *in the first* urine sample.
- Abstinence last: CARD^{TM} did *not* detect *any* analyte that was not attributed to a reported prescription *in the last* urine sample.

Note that "compliance both" implies that "compliance first" as well as "compliance last" were present in both tests from the same individual. The same logic applies to "abstinence both."

The Fisher's exact test was used to evaluate differences in adherence to treatment medications and abstinence rates according to the type of treatment (in-patient vs. out-patient) and level of care. Also, every statistical analysis herein comes with a controlled Type-I error rate.

Results

Part 1. Statistical analysis of first and last urine samples 2010–2011 (n = 1,372)

There is significant (Table 7) statistical evidence that compliant patients are more likely to be abstinent during treatment compared to noncompliant patients. Prescribed bup/nal was present in both the first and last urine samples in 87.7% of the subjects ($n = 1{,}203$), demonstrating strong compliance to the prescribed drug ($p < .0001$). Concomitantly in the same sample, we found that 47.7% ($n = 655$) were still misusing some psychoactive substances during treatment ($p = .0261$). The association between noncompliance to the medication and continued substance misuse during treatment was found to be statistically significant ($p = .0019$).

Subjects who were compliant to the bup/nal prescription were more likely to be abstinent during treatment than the noncompliant subjects ($p = .0012$; odds ratio = 1.69 with 95% confidence interval [1.210, 2.354]).

Compliance with taking bup/nal was found in both the first and last urine specimens of 87.7% of patients ($n = 1{,}203$; $p < .0001$). In the first urine sample, 93.4% of patients ($n = 1{,}282$; $p < .0001$) were compliant and in the last urine sample of 92.4% of patients ($n = 1{,}268$; $p < .0001$). Over the course of two urine specimen collections, it was found that only 1.8% of the patients ($n = 25$) were not complying at all. Compliance was improved in 4.7% of the patients ($n = 65$) who did not comply at first but complied at last. A total of 5.8% of the patients ($n = 79$) showed a deteriorating compliance behavior by complying initially (at first) but not complying at last.

Abstinence was measured in 52.3% of the patients ($n = 717$; $p = .0942$). No nonprescribed psychoactive substances were detected in both urine samples of those patients. Conversely, ($n = 655$) 47.7% of the patients showed in at least one unreported psychoactive substance in at least one urine sample. No illicit psychoactive substance was found in the first urine sample, 69.5% of the patients ($n = 953$; $p < .0001$) while 70.0% of the patients ($n = 960$; $p < .0001$) had no illicit psychoactive substances found in the last urine sample. During the first and last urine specimen collections, 12.8% of the patients ($n = 176$) were not abstinent at all. Improvement in abstinence was shown in 17.7% of the patients ($n = 243$) who were

Table 3. The association between compliance and abstinence.

	Compliance								
	Both			First			Last		
	OR	95% C.I.	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value
Abstinence									
Both	1.69	(1.22, 2.35)	.0015	1.40	(.91, 2.15)	.1247	1.83	(1.22, 2.76)	.0034
First	1.22	(.87, 1.71)	.2545	1.41	(.91, 2.20)	.1230	1.11	(.73, 1.71)	.6200
Last	1.73	(1.24, 2.41)	.0011	1.12	(.71, 1.76)	.6387	2.22	(1.48, 3.33)	.0001

95% CI = Ninety five percent confidence interval

not abstinent at first but were abstinent at the last sample. However, the abstinence of 17.2% of the patients ($n = 236$) deteriorated as they were abstinent at first sample, but not abstinent at last. Table 3 is a comparison of compliance and abstinence.

Significantly, "abstinence both" is more likely for a patient in "compliance both" than not ($p = .0015$). Also, patients are more likely to be in "abstinence last" if they were in "compliance both" ($p = .0011$). "Abstinence both" is more likely than not for patients who were in "compliance last" ($p = .0034$). Also, "abstinence last" is more likely for a patient who were in "compliance last" than not ($p = .0001$). It seems that there is no statistically significant association between "abstinence first" and "compliance both/first/last" or "compliance first" and "abstinence both/first/last."

Table 4 shows the primary drug class used by nonabstinent patients that was found in at least one urine sample of nonabstinent patients ($n = 655$) and the association between that drug type and compliance to MAT. During treatment, from the first and last urine analysis almost 30% of the nonabstinent patients used psychostimulants, 31% used benzodiazepines, and 47% used opioids during treatment. Nicotine use was not considered in this analysis. The odds ratios with the corresponding 95% confidence intervals, estimated any association between the misused drug and compliance to the bup/nal prescription of the nonabstinent patients. As the high *p* values indicate, there was no statistically significant association between the drugs misused and the compliance status.

Table 4. The association between compliance and primary drug class used by nonabstinent patients (part one).

Drug class	*n* (%)	OR	95% CI	*p* value
Psychostimulants	180 (27.5)	.97	(.60, 1.56)	.8996
Hallucinogens (PCP, LSD, etc.)	1 (2)	—	—	.6710
Opioids (antitussives)	308 (47)	.91	(.59, 1.39)	.6670
Benzodiazepines (antianxiety)	203 (31)	1.18	(.74, 1.90)	.4821
Amphetamines	68 (10.4)	.93	(.47, 1.83)	.8257
Cannabinoids	47 (7.2)	.87	(.39, 1.92)	.7286
Ethanol	133 (20.3)	1.40	(.79, 2.48)	.2450

PCP = Phencyclidine; LSD = Lysergic acid diethylamide

Contingency analyses

The results of the contingency analysis of compliance and abstinence as a function of five states (Table 5), treatment modality (Table 6) and a comparison of compliance and abstinence rates in 2010 and 2011 are presented here.

Table 5. Compliance and abstinence rates as a function of the five eastern states.

	Compliance			Abstinence		
State	Both: *n* (%)	First: *n* (%)	Last: *n* (%)	Both: *n* (%)	First: *n* (%)	Last: *n* (%)
MD	65 (75.6)	74 (86.1)	73 (84.9)	36 (41.9)	59 (68.6)	42 (48.8)
ME	303 (87.3)	318 (91.6)	327 (94.2)	171 (49.3)	229 (66.0)	234 (67.4)
NC	65 (83.3)	72 (92.3)	71 (91.0)	36 (46.2)	46 (59.0)	53 (68.0)
RI	150 (86.7)	165 (95.4)	154 (89.0)	87 (50.3)	110 (63.6)	124 (71.7)
VT	620 (90.1)	653 (94.9)	643 (93.5)	387 (56.3)	509 (74.0)	507 (73.7)
χ^2	17.00	13.15	12.74	10.79	15.49	24.27
p value	.0019	.0105	.0126	.0290	.0038	.0001

MD = Maryland; ME = Mein; NC = North Carolina; RI = Rhode Island; SC = South Carolina; VT = Vermont

Table 6. Compliance and abstinence as a function of the patients' treatment modality.

	Compliance			Abstinence		
Modality	Both: *n* (%)	First: *n* (%)	Last: *n* (%)	Both: *n* (%)	First: *n* (%)	Last: *n* (%)
In-patient	27 (75.0)	32 (88.9)	29 (80.6)	15 (41.7)	20 (55.6)	24 (66.7)
Out-patient	1,176 (88.0)	1,250 (93.6)	1,239 (92.7)	702 (52.5)	933 (69.8)	936 (70.1)
χ^2	5.51	1.25	7.43	1.66	15.49	.19
p value	.0190	.2637	.0064	.1972	.0664	.6612

Table 7. Compliance and abstinence rates over level of care.

	Compliance			Abstinence		
Level of care	Both: *n* (%)	First: *n* (%)	Last: *n* (%)	Both: *n* (%)	First: *n* (%)	Last: *n* (%)
IP	10 (71.4)	12 (85.7)	11 (78.6)	7 (50.0)	7 (50.0)	11 (78.6)
RES	17 (77.3)	20 (90.9)	18 (81.8)	8 (36.4)	13 (59.1)	13 (59.1)
IOP	255 (88.9)	275 (95.8)	264 (92.0)	172 (59.9)	230 (80.1)	215 (74.9)
OP	759 (88.0)	801 (92.8)	803 (93.1)	428 (49.6)	571 (66.2)	588 (68.1)
OTP	162 (87.1)	174 (93.6)	172 (92.4)	102 (54.8)	132 (71.0)	133 (71.5)
χ^2	6.11	4.80	7.93	11.98	23.66	6.66
p value	.1911	.3090	.0944	.0175	.0001	.1549

IP = In-patients; IOP = Intensive out-patients; OP = Out-patient; OTP = Opioid treatment programs; RES = Residential facility

There are overall statistically significant differences in the compliance and abstinence rates among the five states. VT exhibited the highest "compliance both" rate of over 90% while Maryland (MD) gave the lowest rate. VT also showed the highest "abstinence both" rate of over 56% while MD the lowest.

There is statistically (Table 7) significant evidence from Fisher's exact tests, to conclude, that out-patients adhere to treatment medications better than in-patients ($p_{\text{both}} = .0257$; $p_{\text{last}} = .0156$). Except for the case of "compliance first" where there was no statistically significant difference between the out-patients and the in-patients ($p_{\text{first}} = .2908$). On the other hand, the abstinence rates were similar between the out-patients and the in-patients.

Among five different levels of care, the overall difference in compliance rates was not found to be statistically significant ($p = .2699$). However, "abstinence first" ($p = .0001$) and "abstinence both" ($p = .0175$) were statistically significant over all levels of care. Although not significant, the in-patients and the patients in the residential facility exhibited the lowest compliance rates. The in-patients showed the greatest improvement with in-patients last and intensive out-patients having the highest abstinence rates while the patients in the residential facility programs gave low abstinence rates consistently.

An annual comparison of compliance and abstinence rates between the years 2010 and 2011 was not statistically significant. Compliance and abstinence during treatment at one facility over the 2 years of the urine sample are presented. Patients ($n = 152$) 11.1% who had both the first and last urine specimens collected in 2010, were compared to patients ($n = 641$) 46.7% who had both specimens collected in 2011. A further regression analysis also found that changes over time were not statistically significant.

Part 2. Longitudinal analysis of all samples tested in 2011 (n = 1,299)

The results of the longitudinal analysis are illustrated in Figures 1 and 2 and Table 8.

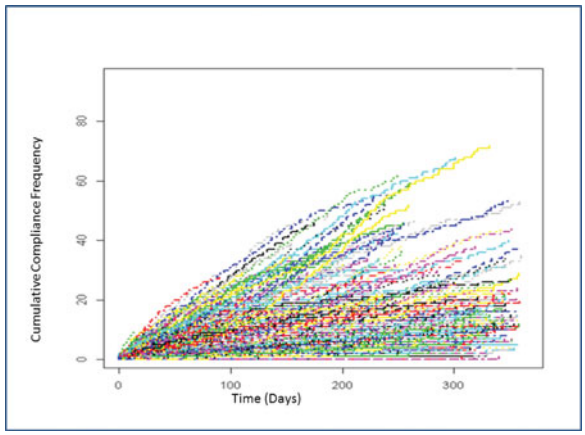

Figure 1. Cumulative compliance frequency over days in 2011.

Figure 1 illustrates a longitudinal trend of compliance in the subset of patients ($n = 1{,}299$) improved compliance rates observed over time are implied by a statistically significant upward trend ($p < 2.2 \times 10^{-16}$).

In Figure 2 the general, overall upward trend observed was statistically significant ($p = 2.2 \times 10^{-16}$), which implies improved abstinence rates over time in the same subset of the patients ($n = 1{,}299$) as is seen in Figure 1.

The number of times a not-reported substance was found in the specimens of $n = 662$ patients was $n = 906$. Some of the nonabstinent patients were polydrug users

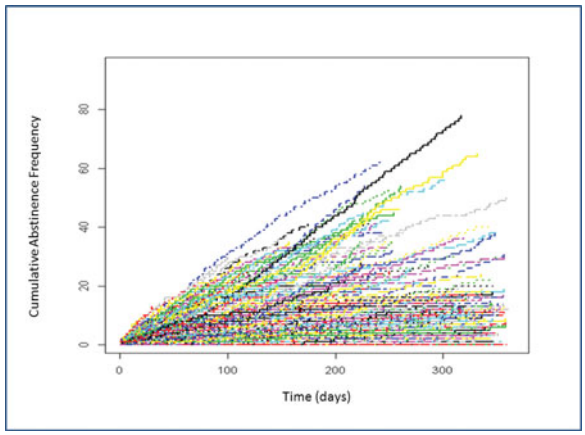

Figure 2. Cumulative abstinence frequency over days in 2011.

Table 8. Primary types drug used by the patients ($n = 662$) 51% who were not abstinent in 2011.

Drug class	($n = 906$) (%)	Drug class	($n = 906$) (%)
Amphetamines	37 (4.0)	Ethanol	61 (6.7)
Barbiturates	9 (1.0)	Hallucinogens	1 (.1)
Benzodiazepines	134 (14.8)	Cocaine	61 (6.7)
Cannabinoids	355 (39.2)	Opioids	248 (27.4)

Notes: Opioids = Semisynthetic opioids such as heroin, oxycodone, and methadone (NAABT).

during treatment. Cannabinoids were found in 39% of samples, opioids 27.4% and benzodiazepines in 14.7%. Nicotine use was not considered in this analysis.

Discussion

These clinically relevant results show that although significant illicit opioid use was present in this cohort (Part 1), a significant reduction of illicit opioid use was demonstrated in the longitudinal analysis (Part 2). Significant strong compliance was shown and should encourage the continued and expanded utilization of bup/nal. However, a study by Balhara & Jain (2012) utilizing urine drug testing in a relatively small sample evaluated patients for 1-year and found that urinalysis failed to detect bup/nal in 44.7% of the samples. In the current experiment, the analysis found much higher compliance to bup/nal, with a noncompliance of 12% overall.

Statistical analysis of the first and last urine samples in this large cohort revealed an almost 50% nonabstinent rate during active treatment. These results are consistent with Bentzley, Barth, Back, & Book, who found that every study they reviewed reported that, 1 month following discontinuation of bup/nal, relapse to illicit opioid use exceeded 50%. Together these results support the routine use of urine drug screening among individuals in programs for treatment for opioid dependence (Bentzley, Barth, Back, & Book, 2015).

A study from Iran provided some evidence that compared to oral naltrexone; the employment of bup/nal was associated with greater number of opioid-negative UDS and better treatment retention (Mokri, Chawarski, Taherinakhost, & Schottenfeld, 2016). Subramaniam et al. (2011) evaluated predictors of abstinence from National Institute on Drug Abuse (NIDA) multisite bup/nal treatment trial in opioid-dependent youth. They found that youth reporting injection drug use, and those receiving adjuvant treatments for additional health problems, were more likely to have a lower opioid use. In another study, the same group looked for predictors of attrition for the duration of bup/nal treatment and found that retention can be improved by giving attention during the first 2 weeks of treatment to medication noncompliance, or an early opioid-positive urine tests (Warden et al., 2012).

The current longitudinal analysis (Part 2) showed that adherent patients had progressive increases in abstinence rates. These results and the above studies confirm the clinical observation that patients who comply with opioid agonist medications are more likely to be adherent to their addiction treatment plan. Cross-sectional data analysis demonstrates that polysubstance use is the norm initially, with longitudinal analysis showing continued improvement of treatment outcome over time. This study has clearly shown, with a 1.70 odds ratio and a very high p value (2.2×10^{-16}), that medication adherence is essential to the successful management of patients in chemical-dependency programs.

The reduction in the use of nonprescribed opioids during treatment, found in the longitudinal analysis (Part 2) of this cohort of bup/nal patients, is significant. When viewed from a harm-reduction perspective, the finding of cannabis in 38% of UDS, and benzodiazepines in 14.1% could be considered a significant accomplishment if they were used rather than opioids.

Compliance rates as high as 92% demonstrate the amelioration of bup/nal diversion in programs, like those in this study, that provide integrated on-site counseling and urine drug testing against known doses of bup/nal. This information should support the elimination of nonstandard-of-care practices, which drive the diversion of buprenorphine in the form of bup/nal.

Limitations

Most drugs are detectable for up to 1–3 days in urine; some like cannabis can be detected after 2 weeks. Urine remains stable over time, can be frozen and is considered a biological hazard for specimen handling and shipping. Urine drug tests are sometimes viewed as psychologically invasive because sample collection is directly observed, to prevent methods that interfere with testing accuracies, such as dilution, adulteration, or urine substitution. An important limitation is that there is no relationship between the dose and urine concentration of a drug (Tam, 2017) and because urinalysis, as utilized here, frequency or extent of drug use cannot be determined.

Initially, the data were cleaned in the preprocessing stage of the analysis. The proportion of missing data was very small since we only observed the first and last specimens per patient in Part 1. Imputation was not advised at that time since it could have caused more biases with few specimens looked at per patient. The longitudinal analysis (Part 2) was based on laboratory data derived from each patient sample tested in 2011. In this subset, the lack of rich clinical correlation prevents

extrapolation of group data to individual patients. For example, due to unknown variations in the testing intervals and drug use frequently among recovering patients, we cannot know, the actual percentage of patients who used opioids. Table 8 represents the percentages of drug types used at the time and frequency at which the samples were taken. Among 622 patients there were 934 instances of unreported drug use. Such limitations should spur further longitudinal research with expanded clinical datasets, aided by the development of more standardized clinical assessment instruments such as the American Society of Addiction Medicine (ASAM) criteria software, genetic analyses, and comprehensive analysis of UDS reporting.

The limitation on extrapolation of group data was avoided in the initial cross-sectional analysis of data from first and last urine samples (Part 1) when 308 of nonabstinent patients were found to be using opioids. However, there could have been a failure to protect against surveillance bias; variations in drug use behaviors on admission and discharge from programs may have influenced this result, for example, discharge against medical advice was not assessed in this study. Other caveats in this study include lack of Type ll power analysis. There were some confounding effects present in the inception cohort; all CARD™ data available from 2010 to 2011. For example, the differential length of follow-up (the number of days between the first and last urine samples varied from 15 to 717 days). Another effect may be that the first urine samples taken following bup/nal combination therapy when high levels of illicit drugs might be present could result in an exaggeration of the improvement seen in the subsequent longitudinal linear trend.

Conclusion

The authors of this article recognize that stabilization of the opioid system by MAT in conjunction with innovative methodologies such as the CARD™ report assists in addiction treatment, engagement, retention, and improved outcomes. Bup/nal in a number and variety of forms (e.g., Suboxone® and Zubsolve®) and methadone, are the available FDA approved MAT for opioid maintenance therapy. The success of the acute use of bup/nal during treatment is qualified by the potential for addiction liability, and the antireward effects of long-term use (Elman, Borsook, & Volkow, 2013; Hill et al., 2013).

Importantly, in this study compliance and abstinence were found to be positively correlated while modality and the level of care are all important factors that impact compliance and abstinence. Outcome studies that include other cofactors such as the length of stay, and experiments that use other tools to access, for example, emotionality measures (Hill et al., 2013) and fMRI to investigate the neural mechanisms that elicit reward-seeking and relapse in addictive behaviors (Volkow, Fowler, Wang, Telang, & Baler, 2009) are encouraged. To further enlighten our understanding of the psychological status of recovering patients, larger studies are required. A planned extension of this work will include a panel of reward gene polymorphic candidates, CARD analysis, the Addiction Severity Index (ASI) and ASAM criteria software in polydrug users attending an in-patient 28-day residential program. We encourage the development of thoughtful new strategies like a pharmacogenetic approach to the treatment of opioid dependence to target the specific brain regions responsible for relapse and opioid addiction (Lawford et al., 2000).

These clinically relevant results, with limitations, showing a significant reduction of illicit opioid use and strong compliance, should further encourage the cautious continued and expanded utilization of to bup/nal (Blum, Gold, Clark, Dushaj, & Badgaiyan, 2016). Meanwhile, the long-term use of bup/nal, because of the potential for addiction liability and antireward effects, requires further intensive investigation (Elman et al., 2013; Hill et al., 2013). We believe that these results will provide active organizations including the National Alliance of Advocates for Buprenorphine Treatment (NAABT) with informative UDS reporting that can help the OUD community in the future.

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Declaration of interest

We declare that the following authors have financial relations with Dominion Diagnostics, LLC: Kenneth Blum PhD; Daryl Inaba, Pharm D; David E Smith; John Femino; and David Han. Mary Hauser, MSc is Vice President of Addiction Services, Dominion Diagnostics, LLC, Scott Saunders, MSc is employed by Dominion Diagnostics, LLC. There are no other conflicts of interest.

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