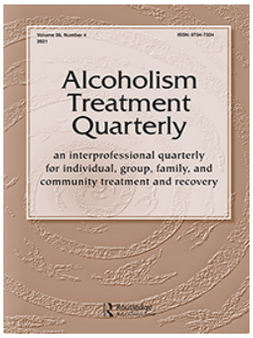

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Profiles and Predictors of Treatment-Resistant Opioid Use Disorder (TROUD): A Secondary Data Analysis of Treatment Episode Data Set's 2017 Admissions

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ABSTRACT

Though behavioral interventions and medications have shown efficacy for individuals suffering from an opioid use disorder (OUD), there is a substantial sub-population that does not respond to currently available treatments. Through a secondary data analysis, this study finds evidence for the existence of treatment-resistant opioid use disorder (TROUD) by determining and examining factors associated with low and high treatment groups. This study provides evidence that failure to successfully complete treatment is related to the disorder's resistance, thereby opening new clinical and research paths that can help in designing personalized therapies to treat TROUD.

KEYWORDS

Substance use disorder; opioid use disorder; treatment resistance; risk factors; predictive models

Introduction

About 2.1 million adults in the United States suffer from opioid use disorder (OUD), a chronic, lifelong, and hard-to-treat disease. While there is no cure for OUD, it can be treated. Between 1999 and 2017, opioid overdose – either subsequent to prescription or consumption of opioids obtained illicitly – has resulted in an estimated 400,000 deaths (Scholl, Seth, Kariisa, Wilson, & Baldwin, 2018). About 130 people die each day from opioid-related use (Centers for Disease Control and Prevention [CDC], 2017). Nearly 70,000 overdose deaths occurred in 2017 (Hedegaard, Warner, & Miniño, 2018) with 47,000 of them directly from opioid use (CDC, 2018). Data from the 2016 National Survey on Drug Use and Health show that about 92 million adults have used an opioid of some kind with about 12 million reporting misuse (Ahrnsbrak, Bose, Hedden, & Lipari, 2017).

Current knowledge of OUD as a disease

National neuroscientists, have consistently stated that addiction is a brain disorder (Brown, Purdon, & Van Dort, 2011; Darcq & Kieffer, 2018; Elman, 2016; Valentino & Volkow,

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2018). Extended opioid use causes irreversible changes to the brain, especially in the dopamine and opioid systems (Gold, Pottash, Extein, & Kleber, 1980). Heroin, methadone, or fentanyl stimulate and overpower the dopamine and opioid systems. These opioid agonists overwhelm the natural actions of endogenous brain systems and receptors by stimulation of reward (Koob, 2006; Volkow, Koob, & McLellan, 2016).

Brain illness

An understanding of OUD's impact on the brain and the theory supporting OUD as being a brain disease can be found in the recent consensus report of the National Academies of Science, Engineering, and Medicine, (National Academies of Science, 2019).

> The altered reward and cognitive processes in combination with the emergence of a chronic stress and negative mood state have been hypothesized to be responsible for a "dark side of addiction" (Koob, 2006), in which the attempts to alleviate negative emotions and the inability to feel pleasure that arise during non-intoxication periods contribute to compulsive drug-taking behavior. A particular component of the brain opioid system—the dynorphin-kappa system—has been strongly implicated in this persistent negative affect which is thought to drive continued drug use, craving, and relapse (Chavkin & Koob, 2016). Moreover, these changes to the brain continue even after an individual discontinues opioid use and no longer has symptoms of acute withdrawal, making long-term recovery more difficult (Leshner, 1997; Volkow, Koob, & McLellan, 2016, p. 30).

The operational changes in the brains of individuals suffering from an OUD are significant and possibly permanent (Carlezon & Thomas, 2009; Koob & Le Moal, 2008; Meredith, Baldo, Andrezjewski, & Kelley, 2008). As with any other brain receptor damage, OUD-related brain damage often results in uncommon or self-destructive behaviors. Any successful treatments for OUD must address both the individual's altered brain and behaviors in conjunction.

Current treatments

OUD treatment is a multifaceted approach including both psychotherapy and medications (National Academies of Science, 2019). Medications are often referred to as medication-assisted treatment (MAT). There are three medications currently approved by the U.S. Food and Drug Administration (FDA) for treating OUD. They are buprenorphine, methadone, and extended-release naltrexone. Buprenorphine is the most commonly prescribed MAT. Several psychotherapeutic treatment modalities have demonstrated their efficacy for treatment retention and completion as well as reduction in overall opioid use.

Treatment-resistant opioid use disorder (TROUD)

Similar to a group of patients with treatment-resistant depression (Conway, George, & Sackeim, 2017; McIntyre et al., 2014), a sub-population exists within the patients suffering from an OUD who do not respond to currently available treatments. The resistance to treatment mostly comes from the disease and not from the patients who are blamed for treatment failure (Conway et al., 2017). In the TROUD model, we are following the success of addressing treatment-resistant depression (TRD), which consists of at least two adequate

treatment attempts without achieving remission. We believe it is time that TROUD should be examined thoroughly for its underlying causes. This exploratory investigation features a secondary analysis approach to examine a subpopulation of individuals suffering from an OUD after multiple past treatment failures.

Hypothesis

Our preliminary work (Patterson Silver Wolf & Gold, 2020) shows the possible existence of TROUD and justifies the need for a deeper understanding of this disorder that is not being treated effectively using current remedies. While this project is hypothesis generating, we postulate that, with an evidence-based approach – i.e., by analyzing a large dataset of patients' admissions into SUD treatment – we will be able to classify TROUD into ranges or sets of profiles that might foretell if a patient would resist the usual treatment.

Methods

Data from the Treatment Episode Data Set (TEDS), specifically the TEDS-A-2017 dataset, were downloaded from the Substance Abuse and Mental Health Data Archive (https://www.datafiles.samhsa.gov/study/treatment-episode-data-set-admissions-teds-2017-nid18473). This dataset includes over 2 million records of individuals who have received care from a substance abuse treatment facility.

Our focus for this study is on those individuals who reported opioid/heroin use and, therefore, patients who reported the following as their primary substance: heroin (code 5), non-prescription methadone (code 6), and other opioids and synthetics, including buprenorphine, codeine, hydrocodone, hydromorphone, meperidine, morphine, opium, oxycodone, pentazocine, propoxyphene, tramadol, and any other drug with morphine-like effects (code 7).

Our intention is to discover what factors may contribute to the likelihood an individual will undergo 5 or more treatments. Thus, our subset of TEDS data was categorized into two groups: one group for those who have received zero to four treatments and one group for those who received 5 or more treatments. We call these two groups the "low treatment" and "high treatment" groups, respectively.

Twelve variables were chosen to study their associations with low and high treatment groups in three separate populations, as follows: opioid/heroin use, opioid (non-prescription methadone and other opioids and synthetics), and heroin use.

The variables of interest were collapsed into fewer, more aggregated categories for analysis. Education was recoded to create two groups: low and high education. The low education category includes those with 8 to 12 years or a GED (codes 1, 2, 3) and high education includes those with 13 to at least 16 years (codes 4 and 5). Employment was also organized into two groups: employed and not employed. The employed category includes those who work full time or part time (codes 1 and 2) and the not employed category includes those with no employment (codes 3 and 4). Two groups were created for living arrangement: homeless/dependent (codes 1 and 2) and independent (code 3). The patient's usual route of opioid administration was categorized as one of two groups as well: injection (code 4) or all other routes (codes 1, 2, 3, 5). In our dataset, the frequency of patient use was coded as daily (code 3) or not daily (code 1, 2). Age at first use was categorized as 20 years

and under (codes 1, 2, 3, 4) or over 20 years of age (codes 5, 6, 7). Whether the patient had co-occurring mental and substance use disorders was left unchanged from the dataset: yes (code 1) or no (code 2). Age at admission was categorized into the following groups: 12–29 years (codes 1, 2, 3, 4, 5), 30–49 years (codes 6, 7, 8, 9), 50–64 years (codes 10, 11), and 65 or more years (code 12). Gender was left unchanged: male (code 1) or female (code 2). Marital status was recoded to create three categories: married (code 2), never married (code 1), and separated/divorced (code 3 and 4). Race was categorized into four categories: American Indian (code 2), White (code 5), Black/African American (code 4), and other (codes 1, 3, 6, 7, 8, 9). Number of days waiting to be admitted to treatment was left unchanged: 0 days (code 0), 1–7 days (code 1), 8–14 days (code 2), 15–30 days (code 3), and 31 or more days (code 4). More detail of this regrouping process can be found in the Appendix.

The opioid/heroin dataset consisted of 607,152 records (135,734 opioid and 471,418 heroin). All missing data were removed to create a final dataset of 249,769 (52,095 opioid and 197,674 heroin) records used for analysis. Population and outcome characteristics were compared between the final records used for analysis and those that were not used due to missing data. We did not observe a significant difference between the two groups.

For univariate analysis, frequency tables with chi-squared tests were completed to determine which variables had an increased frequency in the high treatment group for all three populations separately. For multivariate analysis, logistic regression was used to investigate the effect of variables of interest simultaneously, which allows for a better understanding of which variables increase a patient's chance of unsuccessful treatment attempts. We also calculate the probability of being in the high treatment group using the logistic regression with the parameter estimates for the covariates. We choose the covariate values of the high-risk group based on the ones that produce the highest odds ratios.

Results

Patients who were diagnosed as having an OUD and who received 5 or more treatments were assigned to the high treatment category based on frequency results generated from TEDS data. Figure 1 shows the number of previous treatments as reported by patients. Most patients were entering treatment for the first time. The figure also shows decreasing frequency of previous treatments until the 5 or more option, where responses increased to 119,356, representing a 19.66% TROUD prevalence rate of the OUD population reporting. It should be noted that this frequency analysis was completed previous to removing missing data; therefore, the sample size is larger than that for the subsequent analyses.

Table 1 shows the distribution of variables of interest regarding the opioid/heroin population. Results suggest, for example, that those with a high education vs a low education were more likely to be in the high treatment group. This was also true for those individuals who were homeless, used injection as the route of administration, used daily, started using under 20 years of age, suffered from co-occurring mental and substance use disorders, were between the ages of 12 and 49 at the time of admission, were male, never married, and were of White or other race category. A couple differences were seen in the opioid population in terms of the high-risk covariates, however (see Table 2). The opioid group showed an increased population distribution in the high treatment category among individuals who were admitted for treatment between the ages of 50 and 64 years. This was

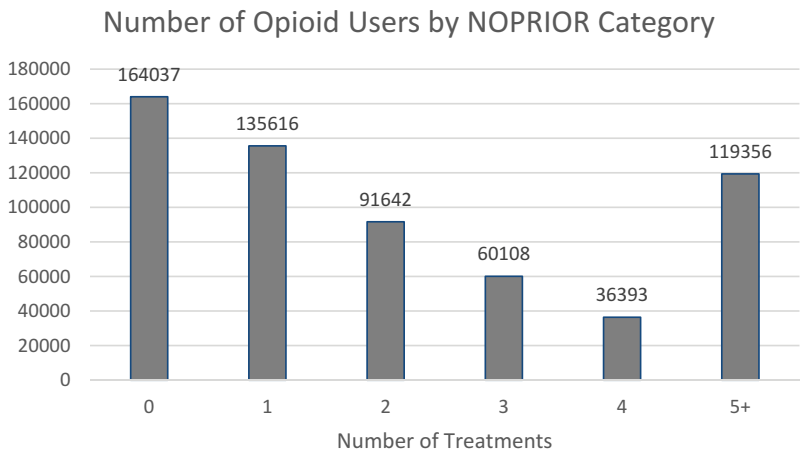

Figure 1. Frequency of the opioid/heroin population and number of previous treatments.

not seen in the entire population or in the heroin group alone (see Table 2). Similarly, the opioid group had an increase among those who were separated/divorced and those who were among the American Indian race category.

Odds ratio results (displayed in Tables 3, 4, and 5) produced from multivariate logistic regression show that people who use injection were more likely to be in the high treatment group. It should also be noted that the homeless/dependent living value for living arrangement in the heroin group (Table 4) is not a significant predictor. Odds ratio results were also used to create high-risk and low-risk groups, described below:

- **Opioid Group (High Risk)**: High education, not employed, homeless/dependent living arrangement, injection as route of administration, use daily, started using at age 20 or under, co-occurring mental and substance use disorders, age 50–64 years at admission, male, never married, other race category.
- **Opioid Group (Low Risk)**: Low education, employed, independent living arrangement, does not use injection as route of administration, does not use daily, started using over age 20, no co-occurring mental and substance use disorders, age 12–29 years at admission, female, married, Black or African American.
- **Heroin Group (High Risk)**: High education, not employed, independent living arrangement (not significant), injection as route of administration, use daily, started using at age 20 and under, co-occurring mental and substance use disorders, age 30–49 years at admission, male, never married, other race category.
- **Heroin Group (Low Risk)**: Low education, employed, homeless/dependent living (not significant), does not use injection as route of administration, does not use daily, started using over age 20, no co-occurring mental and substance use disorders, age 65 + years at admission, female, married, Black or African American.
- **Opioid/Heroin Group (High Risk)**: High education, not employed, homeless/dependent living arrangement, injection as route of administration, use daily, started using at

Table 1. Distribution (%) of the opioid/heroin population into high and low treatment groups.

Variable	High treatment	Low treatment	P-Value
	N (%)	N (%)	
Education			< .0001
Low	40,578 (74.97)	154,258 (78.85)	
High	13,546 (25.03)	41,387 (21.15)	
Employment			< .0001
Employed	7,315 (13.52)	38,928 (19.90)	
Not employed	46,809 (86.48)	156,717 (80.10)	
Living arrangement			< .0001
Homeless/dependent	19,476 (35.98)	60,119 (30.73)	
Independent	34,648 (64.02)	135,526 (69.27)	
Route of administration			< .0001
Injection	41,152 (76.03)	95,928 (49.03)	
Other	12,972 (23.97)	99,717 (50.97)	
Frequency of use			< .0001
Daily	41,018 (75.79)	123,417 (63.08)	
Not daily	13,106 (24.21)	72,228 (36.92)	
First use age			< .0001
≤ 20 years	28,163 (52.03)	83,590 (42.73)	
Over 20 years	25,961 (47.97)	112,055 (57.27)	
Co-occurring mental and substance use disorders			< .0001
No	24,553 (45.36)	109,916 (56.18)	
Yes	29,571 (54.64)	85,729 (43.82)	
Age at admission			< .0001
12–29 years	19,255 (35.58)	68,335 (34.93)	
30–49 years	28,725 (53.07)	96,869 (49.51)	
50–64 years	5,798 (10.71)	27,797 (14.21)	
65+ years	346 (0.64)	2,644 (1.35)	
Gender			< .0001
Female	19,459 (35.95)	79,687 (40.73)	
Male	34,665 (64.05)	115,958 (59.27)	
Marital status			< .0001
Married	3,927 (7.26)	23,099 (11.81)	
Never married	41,980 (77.56)	138,858 (70.97)	
Separated/divorced/widowed	8,217 (15.18)	33,688 (17.22)	
Race			< .0001
American Indian	237 (0.44)	1,204 (0.62)	
White	42,960 (79.37)	143,874 (73.54)	
Black or African American	4,930 (9.11)	36,693 (18.75)	
Other	5,997 (11.08)	13,874 (7.09)	

N = 249,769 (High Treatment = 54,124 and Low Treatment = 195,645). All *P*-Values < .0001

age 20 and under, co-occurring mental and substance use disorders, age 50–64 years at admission, male, never married, other race category.

- **Opioid/Heroin Group (Low Risk)**: Low education, employed, independent living arrangement, does not use injection as route of administration, does not use daily, started using over age 20, no co-occurring mental and substance use disorders, age 65 + years at admission, female, married, Black or African American.

Patients who met all high-risk categories had an overall probability of 65.0% for both the opioid/heroin and heroin group and a 38.3% probability for the opioid group of being in the high treatment group. Patients who met all low-risk categories had an overall probability of 1.5%, 1.7%, and 1.1% of being in the high treatment group for the opioid/heroin, heroin, and opioid groups, respectively.

Table 2. Respective distributions (%) of the Opioid and Heroin Population into High and Low Treatment Groups.

	Opioid group[a]			Heroin group[b]		
Variable	High treatment	Low treatment	P-Value	High treatment	Low treatment	P-Value
	N (%)	N (%)		N (%)	N (%)	
Education			< .0001			< .0001
Low	3,092 (68.56)	35,207 (73.99)		37,486 (75.56)	119,051 (80.41)	
High	1,418 (31.44)	12,378 (yy)		12,128 (24.44)	29,009 (19.59)	
Employment			< .0001			< .0001
Employed	924 (20.49)	12,500 (26.27)		6,391 (12.88)	26,428 (17.85)	
Not employed	3,586 (79.51)	35,085 (73.73)		43,223 (87.12)	121,632 (82.15)	
Living arrangement			< .0001			< .0001
Homeless/dependent	1,314 (29.14)	11,327 (23.80)		18,162 (36.61)	48,792 (32.95)	
Independent	3,196 (70.86)	36,258 (76.20)		31,452 (63.39)	99,268 (67.05)	
Route of administration			< .0001			< .0001
Injection	1,111 (24.63)	7,993 (16.80)		40,041 (80.71)	87,935 (59.39)	
Other	3,399 (75.37)	39,592 (83.20)		9,573 (19.29)	60,125 (40.61)	
Frequency of use			< .0001			< .0001
Daily	2,664 (59.07)	26,216 (55.09)		38,354 (77.30)	97,201 (65.65)	
Not daily	1,846 (40.93)	21,369 (44.91)		11,260 (22.70)	50,859 (34.35)	
First use age			< .0001			< .0001
≤ 20 years	2,211 (49.02)	20,940 (44.01)		25,952 (52.31)	62,650 (42.31)	
Over 20 years	2,299 (50.98)	26,645 (55.99)		23,662 (47.69)	85,410 (57.69)	
Co-occurring mental and substance use disorders			< .0001			< .0001
No	1,763 (39.09)	23,747 (49.90)		22,790 (45.93)	86,169 (58.20)	
Yes	2,747 (60.91)	23,838 (50.10)		26,824 (54.07)	61,891 (41.80)	
Age at admission			< .0001			< .0001
12–29 years	1,395 (30.93)	17,001 (35.73)		17,860 (36.00)	51,334 (34.67)	
30–49 years	2,601 (57.67)	25,656 (53.92)		26,124 (52.65)	71,213 (48.10)	
50–64 years	493 (10.93)	4,574 (9.61)		5,305 (10.69)	23,223 (15.68)	
65+ years	21 (0.47)	354 (0.74)		325 (0.66)	2,290 (1.55)	
Gender			< .0001			< .0001
Female	1,921 (42.59)	22,463 (47.21)		17,538 (35.35)	57,224 (38.65)	
Male	2,589 (57.41)	25,122 (52.79)		32,076 (64.65)	90,836 (61.35)	
Marital status			< .0001			< .0001
Married	520 (11.53)	8,004 (16.82)		3,407 (6.87)	15,095 (10.20)	
Never married	2,983 (66.14)	29,396 (61.78)		38,997 (78.60)	109,462 (73.93)	
Separated/divorced/widowed	1,007 (22.33)	10,185 (21.40)		7,210 (14.53)	23,503 (15.87)	

(*Continued*)

Table 2. (Continued).

	Opioid group[a]			Heroin group[b]		
Variable	High treatment	Low treatment	P-Value	High treatment	Low treatment	P-Value
	N (%)	N (%)		N (%)	N (%)	
Race			< .0001			< .0001
American Indian	53 (1.17)	491 (1.03)		184 (0.37)	713 (0.48)	
White	3,842 (85.19)	39,715 (83.46)		39,118 (78.84)	104,159 (70.35)	
Black or African American	224 (4.97)	4,617 (9.70)		4,706 (9.49)	32,076 (21.66)	
Other	391 (8.67)	2,762 (5.81)		5,606 (11.30)	11,112 (7.51)	

All *P*-Values < .0001.
[a]N = 52,095 (High Treatment = 4,510 and Low Treatment = 47,585).
[b]N = 197,674 (High Treatment = 49,614 and Low Treatment = 148,060).

Table 3. Odds ratio results displaying effect of opioid/heroin population on the high treatment group.

Effect	Point estimate	95% WaldConfidence Limits	
Education: high vs low	1.340	1.309	1.372
Employment: employed vs. not employed	0.729	0.709	0.751
Living arrangement: homeless/dependent vs independent	1.023	1.002	1.046
Route of administration: injection vs other	2.807	2.743	2.872
Frequency of use: daily vs not daily	1.729	1.690	1.768
First use age: ≤ 20 years vs over 20 years	1.454	1.424	1.484
Co-occurring mental and substance use disorders: no vs yes	0.653	0.640	0.667
Age at admission: 12–29 years vs 65+ years	1.061	0.941	1.196
Age at admission: 30–49 years vs 65+ years	1.379	1.225	1.552
Age at admission: 50–64 years vs 65+ years	1.458	1.293	1.644
Gender: female vs male	0.813	0.796	0.830
Marital Status: married vs separated/divorced/widowed	0.798	0.764	0.834
Marital Status: never married vs separated/divorced/widowed	1.217	1.182	1.253
Race: American Indian vs White	0.779	0.674	0.900
Race: Black or African American vs White	0.620	0.598	0.643
Race: Other vs White	1.377	1.331	1.425

It was also observed that number of previous treatments may increase the number of days waiting for treatment (Figure 2). The ordinal logistic regression shows that a larger number of previous treatment is highly associated with longer waiting days for treatment (OR = 1.24, $p < .001$).

Since odds ratio results suggest that patients between the ages of 50 and 64 years at admission are considered high risk for the opioid/heroin population and univariate analysis does not show this age group to be in the high treatment group, we explored what variables in the logistic model may have influenced the univariate result. As shown in Tables 6, 7, and 8, the younger population is more likely to use injection as the route of administration, to never have been married, and to report as being White. These three factors were shown to be highly associated with age at admission; therefore, these patients enter treatment at a younger age, which is why the age group of 12 to 49 years is more likely to be in the high treatment group than the 50 to 64 years category.

Table 4. Odds ratio results displaying effect of heroin population on the high treatment group.

Effect	Point estimate	95% WaldConfidence Limits	
Education: high vs low	1.366	1.332	1.402
Employment: employed vs. not employed	0.737	0.714	0.761
Living arrangement: homeless/dependent vs independent	0.998	0.976	1.021
Route of administration: injection vs other	2.288	2.228	2.350
Frequency of use: daily vs not daily	1.770	1.727	1.814
First use age: ≤ 20 years vs over 20 years	1.522	1.488	1.556
Co-occurring mental and substance use disorders: no vs yes	0.626	0.613	0.639
Age at admission: 12–29 years vs 65+ years	1.132	0.999	1.282
Age at admission: 30–49 years vs 65+ years	1.466	1.296	1.658
Age at admission: 50–64 years vs 65+ years	1.449	1.279	1.641
Gender: female vs male	0.826	0.807	0.845
Marital Status: married vs separated/divorced/widowed	0.814	0.776	0.854
Marital Status: never married vs separated/divorced/widowed	1.157	1.121	1.194
Race: American Indian vs White	0.779	0.659	0.922
Race: Black or African American vs White	0.553	0.532	0.574
Race: Other vs White	1.313	1.267	1.361

Table 5. Odds ratio results displaying effect of opioid population on the high treatment group.

Effect	Point estimate	95% WaldConfidence Limits	
Education: high vs low	1.356	1.268	1.451
Employment: employed vs. not employed	0.779	0.720	0.842
Living arrangement: homeless/dependent vs independent	1.122	1.046	1.204
Route of administration: injection vs other	1.451	1.347	1.563
Frequency of use: daily vs not daily	1.149	1.079	1.224
First use age: ≤ 20 years vs over 20 years	1.305	1.221	1.395
Co-occurring mental and substance use disorders: no vs yes	0.679	0.637	0.723
Age at admission: 12–29 years vs 65+ years	0.958	0.611	1.502
Age at admission: 30–49 years vs 65+ years	1.353	0.866	2.113
Age at admission: 50–64 years vs 65+ years	1.649	1.048	2.594
Gender: female vs male	0.800	0.751	0.853
Marital Status: married vs separated/divorced/widowed	0.735	0.657	0.821
Marital Status: never married vs separated/divorced/widowed	1.172	1.080	1.271
Race: American Indian vs White	1.138	0.853	1.518
Race: Black or African American vs White	0.538	0.468	0.619
Race: Other vs White	1.399	1.250	1.565

Table 6. Distribution of age at admission into race categories for the opioid/heroin population.

Age at admission	American Indian	Black or African American	Other	White	Total
	%	%	%	%	%
12–29 years	0.66	6.40	6.75	86.19	100.00
30–49 years	0.56	13.89	8.49	77.06	100.00
50–64 years	0.42	49.59	9.13	40.86	100.00
65+ years	0.47	63.91	7.86	27.76	100.00

N = 249,769.

Discussion

Public datasets such as TEDS can be useful in discovering trends in medical care practices. These trends have the potential to establish a better understanding of why treatment outcomes differ from patient to patient and from population to population. In this study, we have uncovered evidence that there are factors that have an association with treatment resistance. We observed that if a patient used injection as their route of administration, their

Table 7. Distribution of Age at admission into marital status categories for the opioid/heroin population.

Age at admission	Married	Never married	Separated/ divorced/widowed	Total
	%	%	%	%
12–29 years	5.71	89.31	4.98	100.00
30–49 years	13.30	66.56	20.14	100.00
50–64 years	14.37	52.72	32.91	100.00
65+ years	16.62	43.71	39.67	100.00

N = 249,769.

Table 8. Distribution of age at admission into usual route of administration categories for the opioid/heroin population.

Age at admission	Injection	Other	Total
	%	%	%
12–29 years	62.64	37.36	100.00
30–49 years	55.87	44.13	100.00
50–64 years	32.81	67.19	100.00
65+ years	34.15	65.85	100.00

N = 249,769.

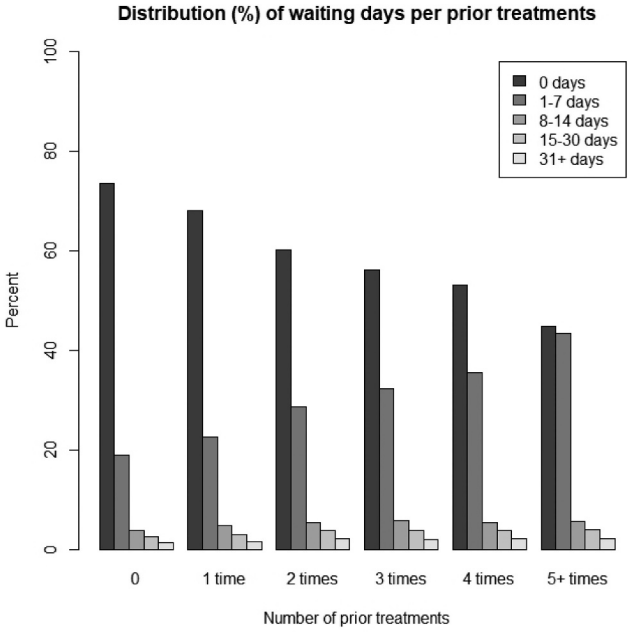

Figure 2. Distribution of number of days waiting per number of previous treatment groups.

chances of repeating treatment attempts 5 or more times were almost 3 times those who used another method of administration.

We also found that if a patient comes to a treatment facility with an opioid or heroin disorder and the patient meets all of the described high-risk categories, the person's chance

of treatment resistance is more than 50%. In addition, those who meet the low-risk category criteria are unlikely to experience treatment resistance.

Patients aged below 50 years at admission tend to use injection as the route of administration almost twice as often as those over 50 years of age, which is highly associated with the risk of treatment resistance. It is noteworthy that data (adjusted by other risk factors) indicate that patients with age at admission between 50 and 64 years are most vulnerable to have treatment resistance. Patients aged 65 years and older show the lowest risk of experiencing treatment resistance.

Shifting the current paradigms of OUD clinical practice

Our treatment industry will have to experience a major change in understanding SUDs in order to consider the idea of a condition such as TROUD. This condition, similar to TRD and other disorders, certainly requires patients' personal commitments to treatment plans. However, treatment failure might have less to do with someone's personal choice to resist OUD treatment and more to do with the disorder's resistance. A certain number of failures has been accepted as the norm throughout the SUD treatment industry along with recycling patients back through the same treatment-as-usual (Crist et al., 2018; Mattick, Breen, Kimber, & Davoli, 2009) especially OUD (Connery, 2015; Klimas et al., 2019). While studies of treatment retention prediction exist in the literature (Acion et al., 2017; DiClemente, Bellino, & Neavins, 1999), proposed models do not address the possibility of certain biopsychosocial conditions that will not respond to any current treatment-as-usual interventions. The intent of this study is to change the long-held above erroneous concepts about these interventions and to establish that TROUD exists and is the result of the disease. As such, it must be addressed separately and with dedication.

Changing the current scientific concept of OUD treatment resistance

In order to conduct both clinical and biological research, the defining criteria for TROUD need to be established (Conway et al., 2017). Hence, the primary question that must be answered is the following: "What causes resistance to OUD treatment?" The current concept throughout the SUD treatment industry is stereotypical – i.e., the term resistant to treatment intuitively refers to the patient's unwillingness or ambivalence about engaging in the treatment process (Miller & Rollnick, 1991). This term is also not understood in the context of a patient's treatment failure after receiving antibiotic treatment for a bacterial infection. Just as challenges accompanied the early research into the clinical process of TRD, similar challenges (Dyck, 1994) will have to be overcome if TROUD is to be worthy of consideration. Conway and colleague (Conway et al., 2017) provided a staged approach to defining TRD. This would offer well-reasoned guidance on how TROUD can be defined. Similar to TRD, TROUD would benefit from having its own original hypotheses, with placebo-controlled study data needed to understand the rationale for targeting specific brain regions or opioid use–related neurological disorders with precision treatments.

Paving the way for innovative OUD treatments

Just as TRD has enabled a larger suite of innovative, tailored treatment options, such as electroconvulsive therapy, ketamine, and breakthrough psilocybin therapy (Patterson Silver Wolf & Gold, 2020), this exploratory project will open new clinical and research paths and will help to design personalized therapies to treat the serious condition of TROUD.

Limitations

While there are important findings in this study, there are also limitations. Without having any data related to specific treatment services received or whether treatment recommendations where clinically satisfied, it is difficult to determine whether treatment as usual was impactful with sample population. Further, those who inject opioids are considered higher risk for repeated treatment attempts. Without having follow-up on the people in their 1st, 2nd, 3rd, or 4th treatment who never return to treatment, it is unclear that these characteristics really tell us what is proposed in this study. Are these just individuals earlier in their OUD who will later reach 5 or more treatments? Seemingly many of the 1–4 treatment individuals will end up at 5 + eventually, but there is no way for us to know that with this data. There is a need to go beyond existing data analysis into qualitative case study research were researchers can understand the treatment histories of patients as well as other bio-psycho-social conditions that could be associated with TROUD (treatment recycling).

Conclusion

The current treatment-as-usual system does not work for a sub-population of OUD patients, regardless of the number of readmissions, as the existing clinical paradigm considers OUD a chronically relapsing disorder. Our study challenges the notion of the patient's failure and establishes many of the failures are due to the disorder's resistance and not the patient's resistance or personal choice not to engage in treatment. Our results show that as previous treatments increase, the days waiting to reenter treatment increases, suggesting a pervasive attitude among treatment providers that relapse is the fault of the patient and that they are not as deserving of quick admissions as others with few prior treatment attempts, rather than indicating that the patient has a serious, untreated illness.

During regular biopsychosocial assessments at treatment admission, our new predictive models can alert the clinical team to factors that are associated with failure and the necessity to implement customized interventions and treatment plans. This new concept will facilitate OUD treatments to be personalized to the patient's biology and current conditions and will urge the need to formulate strategies to circumvent known risk factors that lead to failure. For example, if a medication has helped patients with a similar profile or someone is averse to a particular medicine, our predictive tool can alert to adjust the treatment of motivational interviewing, cognitive behavioral therapy or 12-step facilitation and can recommend to include or exclude medication. Many similar adjustments are expected, leading to personalized therapy. Further, more resources can be allocated for vulnerable groups such as people between the ages of 50 and 64 years. Also, some long-term studies may be needed to evaluate efficacy of various strategies (novel treatment or different intensities) that may reduce the treatment resistance for the

vulnerable groups. Some attributes of high risk may be handled better by changes in treatment strategies.

As with other chronic, hard-to-treat, and fatal illnesses, relapse is the indication of an ineffective treatment plan, not the lack of motivation or fault of the patient. In practical reality, those who continue to seek SUD treatment after previous treatments should be viewed as being resilient and in search of relief from a serious disorder. Rather than failure being placed at the feet of the patient who returns to treatment after relapse, failure, like all other illnesses, should be couched in the ineffective treatment plan. It is the treatment that must be changed, not the victims who suffer from this illness.

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Appendix. Variables re-defined

Item	Variable name	Label	Combined values	New categories
Number of previous substance use treatment episodes	NOPRIOR	No prior treatment episodes – 0 One prior treatment episode – 1 Two prior treatment episodes – 2 Three prior treatment episodes – 3 Four prior treatment episodes –4 Five prior treatment episodes –5	0–4 5	0–4 treatments 5+ treatments
Substance use at admission (primary)	SUB1	None –1 Alcohol –2 Cocaine/crack –3 Marijuana/hashish – 4 Heroin – 5 Non-prescription methadone – 6 Other opiates and synthetics – 7 PCP – 8 Other hallucinogens –9 Methamphetamine –10 Other amphetamines – 11 Other stimulants – 12 Benzodiazepines – 13 Other non-benzodiazepines Tranquilizers – 14 Barbiturates – 15 Other non-barbiturate sedatives or hypnotics – 16 Inhalants –17 Over-the-counter medications – 18 Other – 19	5 6–7	Heroin Opioids
Education	EDUC	8 years or less – 1 9–11 years –2 12 years (or GED) – 3 13–15 years – 4 16 or more years – 5	1–3 4-5	Low education High education
Employment	EMPLOY	Full time – 1 Part time – 2 Unemployed – 3 Not in labor force –4	1–2 3–4	Employed Not employed
Living arrangements at admission	LIVARAG	Homeless – 1 Dependent living – 2 Independent living – 3	1–2 3	Homeless/ dependent Independent
Usual route of administration (primary substance)	ROUTE1	Oral – 1 Smoking – 2 Inhalation – 3 Injection – 4 Other – 5	4 1–3,5	Injection Other
Frequency of use at admission (primary substance)	FREQ1	No use in the past month – 1 Some use – 2 Daily use – 3	1–2 3	Not daily Daily
Age at first use (primary substance)	FRSTUSE1	11 years and under – 1 12–14 years – 2 15–17 years – 3 18–20 years – 4 21–24 years – 5 25–29 years – 6 30 years and older – 7	1–4 5-7	≤ 20 years Over 20 years
Co-occurring mental and substance use disorders	PSYPROB	Yes – 1 No – 2	1 2	Yes No

(*Continued*)

(Continued).

Item	Variable name	Label	Combined values	New categories
Age at admission	AGE	12–14 years –1 15–17 years – 2 18–20 years – 3 21–24 years –4 25–29 years – 5 30–34 years – 6 35–39 years – 7 40–44 years – 8 45–49 years – 9 50–54 years – 10 55–64 years – 11 65 years and older – 12	1–5 6-9 10–11 12	12–29 years 30–49 years 50–64 years 65+ years
Biologic sex	GENDER	Male – 1 Female – 2	1 2	Male Female
Marital status	MARSTAT	Never married – 1 Now married – 2 Separated – 3 Divorced/widowed – 4	1 2 3-4	Never married Married Separated/ divorced/ widowed
Race	RACE	Alaska Native (Aleut, Eskimo, Indian) – 1 American Indian (other than Alaska Native) – 2 Asian or Pacific Islander – 3 Black or African American – 4 White – 5 Asian – 6 Other single race – 7 Two or more races – 8 Native Hawaiian or Other Pacific Islander –9	2 4 5 1,3,6–9	American Indian Black or African American White Other