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Non-fatal overdose in the 12 months following treatment for substance use disorders

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Abstract

Background—Overdose (OD) is a leading cause of mortality and morbidity for individuals with substance use disorders (SUDs), and there are limited prospective data on OD during the months following treatment for SUDs.

Methods—Variables associated with an OD in the 12 months after leaving an initial treatment episode were examined in an analysis of the Drug Abuse Treatment Outcomes Study (DATOS), a longitudinal naturalistic multisite study. Participants included 2,966 patients with one or more SUDs. Non-fatal OD was ascertained by a positive response to “In the past 12 months, have you overdosed on drugs?” Multivariate logistic regression analyses were used to identify variables associated with OD.

Results—By 12 months, 93 (3.1%) participants reported one or more ODs. Variables associated with OD were lifetime history of OD, injection drug use (IDU), male sex, greater pain, and history of sexual abuse.

Conclusions—OD-risk appears to be increased by IDU, lifetime OD, sexual abuse history, and pain. The latter finding is novel for a prospective report and requires further study.

Keywords

epidemiology; overdose; treatment; risk factors; sexual abuse; intravenous drug abuse

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Conflict of Interest All authors declare that they have no conflicts of interest.

1. Introduction

Unintentional injury and suicide are the 5th and 11th overall leading causes of death in the U.S. Overdoses (ODs) are major contributors to these outcomes, representing the 2nd leading cause of unintentional injury-related deaths and the 3rd leading cause of death by suicide (Centers for Disease Control and Prevention, 2008). ODs that do not result in death also contribute to significant physical morbidity that often require expensive treatment including peripheral neuropathy, pulmonary edema, arrhythmia, acute cardiomyopathy, hemoglobinemia, rhabdomyolysis, and hypoxia (Warner-Smith et al., 2001; Warner-Smith et al., 2002). Fatal and non-fatal ODs therefore represent major public health burdens. Increases over the past decade in the abuse of prescription opioids (Compton and Volkow, 2006), fatal opioid-related ODs (Ballesteros et al., 2003; Paulozzi, 2006), non-fatal ODs in cocaine users (Kaye and Darke, 2004), and non-fatal ODs in polysubstance users (Darke et al., 2005), support that the burden is growing.

1.1 Risk Factors for OD

At a basic level, a "risk factor" is a "measurable characterization of each subject in a specified population that precedes the outcome of interest and which can be used to divide the population into 2 groups (the high-risk and the low-risk groups…)" (Kraemer et al., 1997, p. 338). Knowledge of risk-factors can facilitate the identification of individuals at elevated risk for OD, and inform both the development of interventions for high-risk patients and prevention efforts. Until recently, with rare exception (Ravndal and Vaglum, 1999), data on risk factors for OD among individuals with SUDs were based on cross-sectional reports using individuals with heroin and other opioid use disorders (e.g., Conner et al., 2007; Darke and Ross, 2000; Darke et al., 2000). These data are constrained by the limitations of cross-sectional risk-factor research (Kraemer, 2003), and unclear generalization to other SUD populations at high risk for OD including cocaine (Kay and Darke, 2004) and polysubstance drug users (Darke et al., 2005).

We were only able to identify a limited number of published, prospective reports of risk factors for non-fatal OD among adult SUDs published in the past 10 years. Two studies examined risk-factors among mixed samples of SUDs (Ravndal and Vaglum, 1999; Wines et al., 2007), one among polysubstance IDUs (Kerr et al., 2007), and one among heroin users (Darke et al., 2005). These studies showed that substance use variables such as opioid use (Kerr et al., 2007; Ravndal and Vaglum, 1999), alcohol use (Kerr et al., 2007), polydrug use (Darke et al., 2005), binge drug use (Kerr et al., 2007), and history of OD (Darke et al., 2005; Wines et al., 2007) predicted OD. Demographic characteristics including white race (Wines et al., 2007), situational factors such as incarceration and homelessness (Kerr et al., 2007), and psychological features such as depressive symptoms (Wines et al., 2007) also increased risk for ODs. Past treatment including previous number of treatment episodes (Darke et al., 2005) and months in inpatient treatment (Kerr et al., 2007) were associated with increased risk, while prospective treatment such as methadone maintenance (Darke et al., 2005; Kerr et al., 2007), residential rehabilitation, and number of treatment days (Darke et al., 2005) reduced risk. IDU drug use variables such as the injection of opioids, cocaine, and speedball (heroin and cocaine), requiring help injecting, and street injection all increased risk (Kerr et al., 2007).

1.2 The Present Study

The present study is a secondary analysis of the Drug Abuse Treatment Outcome Study (DATOS; Hubbard et al., 1997), a longitudinal naturalistic multisite investigation examining the effectiveness of community treatments for SUDs. Our primary aim was to determine variables identified at treatment entry that were predictive of OD in the 12 months following treatment for SUDs. Based in part on previous longitudinal reports, we hypothesized that

history of OD, opioid use, polydrug use, and IV drug use would predict OD after treatment. In particular, we sought to better characterize the magnitude of OD-risk that is independently associated with IV use. We included history of suicidal ideation and suicide attempts in the statistical models as covariates because they are potent risk factors for suicide attempts among treated SUDs, many of which are intentional ODs (Conner et al., 2007; Ilgen et al., 2007). Physical and sexual abuse were included as they are prevalent among individuals in treatment for SUDs and had only been included in one prospective report, which found a relationship for sexual abuse (Wines et al., 2007). Pain was also included in an exploratory analysis as it is prevalent among individuals in substance abuse treatment (i.e., Rosenblum et al., 2003), is associated with the prescription opioids which are associated with OD (Paulozzi et al., 2006), and had not been examined in previous prospective studies. DATOS was selected to accomplish these aims because it is prospective, includes a diverse sample of SUD diagnoses, provides broad coverage of risk and protective factors, and uses a naturalistic study design that enhances generalizability.

2. Method

2.1 Participants and Data Collection

For a more detailed explanation of the methods used for DATOS, please see prior reports (Flynn et al., 1997; Hubbard et al., 1997). Summarizing the methods, treatment programs were selected to maximize generalization to programs in mid-to-large urban areas in the United States. Programs included outpatient methadone treatment, long-term residential, outpatient drug-free, and short-term inpatient. Patients were informed that participation was voluntary and that their decision would not affect their treatment and that their data would not be revealed to treatment providers. The sample consisted of 10,010 patients from 96 programs in 11 cities. Two intake interviews were administered to and completed by 8,109 participants. Patients in the follow-up sample were chosen from programs with greater than 20 participants. The 4,229 eligible participants were stratified by program and treatment duration of less than or more than 3 months (1 month for short-term inpatient). To ensure substantial treatment was received by the majority of follow-up participants, a greater proportion was chosen from the over 3 month (1 month for short-term inpatient) strata. The follow-up sample consisted of 1,000 participants from each treatment modality. Participants were interviewed 12 months after treatment was completed, with the exception of 355 outpatient methadone treatment patients who were still in treatment during the follow-up period and were interviewed approximately 24 months after admission. Of the 3,147 (74%) participants located for follow-up, 2,966 (94.2%) were interviewed, 117 (3.7%) refused the interview, and 64 (2.0%) died by unknown causes.

2.2 Measures

The assessment protocol consisted of widely used instruments including the Addiction Severity Index (McLellan et al., 1992), the Structured Clinical Interview for DSM-III-R (Spitzer et al., 1989), and several substance use and behavioral variables that were based on standard measures used in the Treatment Outcome Prospective Study (Hubbard et al., 1988; Hubbard et al., 1989). Reliability and validity of these measures has been established with clinical populations of substance users (Hubbard et al., 1984; Kranzler et al., 1996; Makela, 2004). Additional self-report measures of drug use administered in DATOS were validated prior to data collection (Flynn et al., 1995).

2.2.1 Dependent Variable—For all analyses, presence or absence of non-fatal OD served as the dependent variable. Participants were asked, “In the past 12 months, have you overdosed on drugs?”

2.2.2 Independent Variables (Baseline)—Non-substance use variables were dichotomized into marital status (divorced, widowed, separated or never married vs. married or living as married), presence or absence of criminal justice involvement, and presence or absence of a lifetime history of physical abuse, sexual abuse, depression, suicidal ideation, and suicide attempt. Prior history of OD, assessed with the question "Have you ever overdosed on drugs?" was categorized as present or absent. The presence of a major depressive disorder was derived using DSM-IV criteria (American Psychiatric Association, 1994). The suicidal ideation item asked "In your lifetime, have you ever thought a lot about ending your life or committing suicide?" The suicide attempt item asked "In your lifetime, have you ever attempted suicide?" Intravenous drug use (IDU) in the 12 months prior to admission was dichotomized into present or absent.

Six SUD and SUD treatment-related variables were created including a four category treatment experience variable that included outpatient drug-free (reference group), outpatient methadone treatment, long-term residential, and short-term inpatient (Hubbard et al., 1997). Preferred substance of use was categorized into four mutually exclusive categories, cocaine (ref), opioid, alcohol, "other." Frequency of use of cocaine, alcohol, and opioids were categorized into none (ref), less than daily, and daily or more.

A continuous polysubstance use variable (ranging from 0 to 8) was created to reflect the number of different drugs (alcohol, cocaine, etc.) used on a weekly basis or more. An additional continuous variable was the count of the number of drug treatments prior to admission into current treatment. Pain was assessed with the item, "during the 12 months before your admission, would you say that your physical or bodily pain was … ?" Responses (ranging from 0 = none, 1 = very mild, 2 = mild, 3 = moderate, 4 = severe) were scored on a continuous scale.

2.3 Statistical Analyses

Univariate analyses were used to identify variables that showed independent associations with OD for initial inclusion in a multivariate logistic regression (Hosmer and Lemeshow, 1989). The Hosmer-Lemeshow statistic was used to evaluate model fit, and odds ratios with 95% confidence intervals were derived using the method of maximum likelihood (Hosmer and Lemeshow, 1989). Listwise deletion was used to eliminate participants that were missing data on any of the predictors. Variables that were identified in univariate analyses as predicting OD with a probability value less than .05 were included in the multivariate analysis. Backwards elimination, entering all variables and removing them one at a time depending on their significance (p-value), was used to trim independent variables to avoid potential biases of forward selection procedures (Hosmer and Lemeshow, 1989). All variables with a probability value of greater than .10 were removed from the analyses.

Listwise deletion was used to eliminate participants that were missing data on any of the predictors. Of the 2,966 participants in the total sample, 77 (2.6%) were excluded from the multivariate analysis due to missing data. Participants who were excluded did not differ on socio-demographic variables at a statistically significant level from participants who were included. They were, however, more likely to make a suicide attempt, X^2 (1, N = 2,944) = 6.61, p = .01. Differences in heroin use, X^2 (2, N = 2,962) = 5.33, p = .07), and treatment modality, X^2 (3, N = 2,966) = 7.03, p = .07), approached but did not achieve significance.

3. Results

3.1 Univariate Analyses

Ninety-three (3.1%) participants reported OD in the 12 months following treatment. In univariate analyses of predictors of OD collected at baseline (Table 1), white race, lifetime

OD, lifetime injection drug use, less than daily opioid use and daily or more opioid use, outpatient methadone treatment, long-term residential treatment, lifetime suicidal ideation, lifetime suicide attempt, sexual abuse, physical abuse, opioid as preferred drug, lifetime major depressive episode, polydrug use, greater pain, and a higher number of drug treatments were associated with OD.

3.2 Multivariate Analyses

The multivariate model provided adequate fit, [$X^2(8, 125) = 11.84$, $p = .16$, Nagelkerke $R^2 = .14$]. In the model (Table 2), lifetime OD (OR, 95% CI; 2.78, 1.74–4.46), IV drug use (2.54, 1.51–4.25), sexual abuse (1.94, 1.17–3.2), male sex (1.91, 1.13–3.22), and pain (1.26, 1.07–1.49) were associated with a higher probability of OD. Polysubstance use showed a trend level association with OD (1.17, 1.00–1.39; $p = .07$).

4. Discussion

The finding that IDU confers risk for OD using a prospective research design extends the results of several cross-sectional studies that supported that IDU increased risk for OD (Brugal et al., 2002; Gossop et al., 1996; Powis et al., 1999). As many of the previous investigations were cross-sectional in nature and/or limited to injectors, we sought to better characterize the magnitude of the OD-risk associated with IDU. In our study, IDU independently increased the risk of future OD more than 2.5-fold. Injection introduces a bolus of the drug(s) directly into the blood stream and the resulting concentration of drug(s) may increase risk for OD. Much of the OD literature focuses on heroin users (Darke and Zador, 1996; Darke and Ross, 2000; Darke et al., 2000; Darke et al., 1996a; Darke et al., 1996b; Darke, 1999). However, in one study up to 98% of non-fatal heroin ODs were a result of injection (Gossop et al., 1996), supporting the significance of this route of administration. The generalizability of this finding to fatal ODs is unclear, and there is a paucity of prospective research on fatal ODs. However, IV use has been found to be associated with fatal ODs in numerous studies (Darke and Zador, 1996; Darke and Ross, 2000; Darke et al., 2000; van Ameijden et al., 1999), and one study suggested that up to 99% of fatal heroin ODs were a result of injection (Darke et al., 2000).

Opioid use did not confer risk for OD in the multivariate analysis, contrary to what had been found in previous studies (Kerr et al., 2007; Ravndal and Vaglum, 1999). To investigate further, we conducted post-hoc analyses to evaluate the interrelations among opioid use, IDU, and OD. We found that 73.4% of opioid users had also been injection users and that only IDU significantly predicted OD when both were entered into the multivariate logistic regression. It is likely that previous studies found an effect for opioid use because they did not include IDU in their analyses (Ravndal and Vaglum, 1999), or exclusively consisted of IDUs (Kerr et al., 2007). When integrated, the literature suggests that injection opioid use in particular increases risk for OD.

Lifetime OD also predicted future OD underscoring that OD is prone to be repeated, and obtaining a history of OD provides important risk-related information (Darke et al., 2005; Wines et al., 2007). Individuals who had difficulty determining a physiologically tolerable dose in the past may be at risk to do so again, particularly when they are using more than one drug (Darke and Ross, 2000), or they experience reduced tolerance due to a disruption of regular drug use (Seaman et al., 1998). It can also be argued that repeated ODs reflect intent to harm or kill oneself, or a suicide attempt. However, neither history of suicide ideation nor attempts was associated with OD in our analysis, suggesting that intentional OD alone is unlikely to explain the finding.

Pain increased OD-risk in our study, a novel finding for a prospective report. Individuals with SUDs who are in physical pain may alter or increase their drug use thereby increasing their

risk for OD (Rosenblum et al., 2003). The risk associated with pain highlights the importance of adequate assessment and treatment of pain in individuals with SUDs (Kuehn, 2009). Research examining the mechanisms through which pain is associated with OD may assist in the development of preventive interventions. Need for prevention efforts may be growing as it has been argued that the increasing use of prescription opiates to manage pain may be partially responsible for the increase in methadone-related deaths (Graham et al., 2008; Streltzer and Johansen, 2006), potentially contributing to a "national epidemic of drug poisoning deaths (p. 618)" (Paulozzi et al., 2006).

Our finding that sexual abuse increased risk for OD is consistent with other studies (Coll et al., 1998; Coll et al., 2001; Wines, et al., 2007). Sexual abuse has prospectively been found to be associated with more severe psychiatric problems in individuals with SUDs (Schneider et al., 2008) and the abuse of substances for self-medicating purposes may increase risk for OD.

Men were at greater risk for OD than women in the multivariate analysis. This finding was not observed in previous prospective studies and was not hypothesized and is interpreted with caution. Sex differences in OD among treated substance abusers are a nascent research area that warrants further study.

The findings suggest that substance use treatment should address OD risk by assessing for and providing education about risk factors, including prior history of OD and IDU. Effective preventive interventions are needed and the potential usefulness of modifying prescription drugs to block their euphoric effect when they are injected rather than ingested orally (True et al., 1988) should be considered. Controversial approaches such as distributing opiate antagonists and educating patients in their use (Baca and Grant, 2005; Piper et al., 2008), and instructing patients on the `safe' use of drugs (Darke and Hall, 2003) may also be worth debating.

4.1 Limitations

There were limitations that are important to acknowledge. There was no elaboration on the definition of OD in the interview manual, leaving it open to the respondents' interpretation. The question did not distinguish illicit from legal drug overdoses or intentional from unintentional overdoses. These issues were also not addressed with additional questions. The absence of data on intentionality in particular is a limitation. Although providing more direction to the interviewer and subject would have been more optimal, it is important to note that there is no widely accepted operational definition of non-fatal overdose on which to base such instructions. Some studies do not define OD and others require respondents to report emergency medical treatment (Wines et al., 2007) or specific drug-related symptoms (Darke et al., 2005) as confirmation that the event was an OD. It is difficult to compare findings across studies that employ different definitions and further research including rigorous psychometric testing of various definitions of OD is needed (Wines et al., 2007).

The prevalence of OD of 3.1% at 12-month follow-up was lower than previous prospective studies wherein prevalence rates ranged from 12% to 29% over 12 months to 5 years (Darke, Williamson, Ross, and Teesson, 2005; Kerr et al., 2007; Ravndal and Vaglum, 1999; Wines et al., 2007). Although there is no clear explanation for the lower prevalence compared to prior reports, a contributing factor may have been the broad range of SUDs (i.e., primary alcoholism) in the study population compared to prior reports that used select populations likely to be at higher risk for OD, for example IDUs (Kerr et al., 2007) and heroin users (Darke et al., 2005). The exclusion of 64 (2%) participants due to death by unknown causes may have also contributed. A significant number of these individuals may have died by OD, which could have impacted both prevalence and risk factor analyses.

Patients in outpatient methadone treatment completed follow-up interviews 24 months after the start of treatment indicating a different follow-up period, and so validity of comparisons with this group is uncertain. In this study, outpatient methadone and inpatient residential treatment were associated with an increased risk for OD in univariate but not in multivariate analyses. This discrepancy may be attributable to outpatient methadone and inpatient residential treatment being confounded with risk factors for OD including a history of prior OD and IDU.

Suicide attempts were also assessed with a single item and did not include a definition of suicide attempts. As a result, suicide attempts with intent to die were not differentiated from non-suicidal self-injury. Participants who were excluded from the study were more likely to make a suicide attempt than those who were included. The relatively small number of excluded individuals minimizes the potential impact of this difference.

4.2 Conclusion

This study was a secondary analysis of a large, multisite, prospective study of SUDs that examined risk factors for non-fatal OD in the 12 months following an initial treatment episode. Independent variables were carefully selected based on the available literature and clinical experience and provide rigorous covariate coverage. Key findings were that recent IV drug use, lifetime OD, sexual abuse history, and pain as determined at treatment entry were associated with OD during the 12-month follow-up.

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Table 1

Baseline Univariate Predictors of OD in 12 Months after Treatment (N=2,966)

Baseline Variables	N (%) or Mean (SD)	OR (95% CI)
Age	33.6 (7.43)	1.02 (.99–1.05)
Sex		
Male	1,909 (64.4%)	1.37 (.87–2.16)
Female	1,057 (35.6%)	1.00
Race/Ethnicity		
Minority	1,764 (59.5%)	.48 (.31–.72)**
White	1,202 (40.5%)	1.00
Married		
Yes	977 (32.9%)	.80 (.52–1.22)
No	1,984 (66.9%)	1.00
Homeless		
Yes	94 (3.2%)	1.05 (.33–3.40)
No	2863 (96.5%)	1.00
Criminal justice status		
Yes	1,319 (44.5%)	1.03 (.68–1.56)
No	1,642 (55.4%)	1.00
Sexual abuse		
Yes	696 (23.5%)	2.02 (1.31–3.10)**
No	2265 (76.4%)	1.00
Physical abuse		
Yes	991 (33.4%)	1.91 (1.26–2.89)**
No	1971 (66.5%)	1.00
Pain	1.47 (1.34)	1.45 (1.24–1.69)***
Preferred drug		
Opioid	830 (28.0 %)	1.96 (1.25–3.06)**
Alcohol	286 (9.6%)	.51 (.18–1.45)
Other	409 (13.8%)	.81 (.39–1.70)
Crack/Cocaine	1,369 (46.2%)	1.00
Cocaine use		
Daily or more	841 (28.4%)	1.72 (.96–3.10)
Less than daily	1287 (43.4%)	1.56 (.90–2.73)
None	832 (28.1%)	1.00
Opioid use		
Daily or more	856 (28.8%)	2.92 (1.84–4.64)***
Less than daily	338 (11.4%)	2.68 (1.45–4.94)***
None	1763 (59.4%)	1.00
Alcohol use		
Daily or more	551 (18.6%)	1.06 (.62–1.82)

Baseline Variables	N (%) or Mean (SD)	OR (95% CI)
Less than daily	1675 (56.5%)	.70 (.36–1.38)
None	731 (24.6%)	1.00
# Drugs used weekly	1.81 (1.16)	1.48 (1.27–1.73)***
IV drug use		
Yes	896 (30.2%)	4.73 (3.05–7.34)***
No	2041 (68.8%)	1.00
Treatment Modality		
LTR	676 (22.8%)	2.20 (1.05–4.59)*
STI	799 (26.9%)	2.02 (.97–4.16)
OMT	727 (24.5%)	3.75 (1.90–7.40)***
ODF	764 (25.8%)	1.00
# Drug treatments	2.06 (3.8%)	1.04 (1.01–1.08)*
Depression		
Yes	1412 (47.6%)	1.80 (1.16–2.80)**
No	1430 (48.2%)	1.00
SI ever		
Yes	957 (32.3%)	1.71 (1.12–2.60)*
No	1,999 (67.4%)	1.00
SA ever		
Yes	548 (18.5%)	2.16 (1.39–3.38)**
No	2,396 (80.8%)	1.00
OD ever		
Yes	701 (23.6%)	4.98 (3.26–7.60)***
No	2259 (76.2%)	1.00

Note. LTR = long-term residential, STI = short-term inpatient, OMT = outpatient methadone treatment, ODF = outpatient drug free, SI ever = history of suicidal ideation, SA ever = history of suicide attempts.

* $p < .05$

** $p < .01$

*** $p < .001$

Table 2

Multivariate Logistic Regressions of OD at 12 Month Follow-up Using Baseline Variables (N = 2900)

		Model 1
Baseline Variables	**Strata**	**OR (95% CI)**
Age (continuous)		1.00 (.96–1.02)
Sex	Male	1.91 (1.13–3.22)*
	Female	1.00
Race	Minority	.81 (.51–1.28)
	White	1.00
Sexual abuse	Yes	1.94 (1.17–3.2)*
	No	1.00
Pain (continuous)		1.26 (1.07–1.49)**
Polydrug use (continuous)		1.17 (0.99–1.39)
IV drug use	Yes	2.54 (1.51–4.25)***
	No	1.00
OD ever	Yes	2.78 (1.74–4.46)***
	No	1.00

Note: OD ever = history of overdose, SI = suicidal ideation. Wald tests were used for significance testing (df = 1).

†= Depressed mood or anhedonia

* $p < .05$

** $p < .01$

*** $p < .001$