Risk Factors for Overdose in Treatment-Seeking Youth With Substance Use Disorders

Amy M. Yule, MD[a,b,c,*]; Nicholas W. Carrellas, BA[a]; Maura Fitzgerald, MPH[a]; James W. McKowen, PhD[a,c]; Jessica E. Nargiso, PhD[b,c]; Brandon G. Bergman, PhD[b,c]; John F. Kelly, PhD[b,c]; and Timothy E. Wilens, MD[a,b,c]

ABSTRACT

Objective: Overdoses (ODs) are among the leading causes of death in youth with substance use disorders (SUDs). Our aim was to identify the prevalence of OD and characteristics associated with a history of OD in youth presenting for SUD outpatient care.

Methods: A systematic retrospective medical record review was conducted of consecutive psychiatric and SUD evaluations for patients aged 16 to 26 years with *DSM-IV-TR* criteria SUD at entry into an outpatient SUD treatment program for youth between January 2012 and June 2013. Unintentional OD was defined as substance use without intention of self-harm that was associated with a significant impairment in level of consciousness. Intentional OD was defined as ingestion of a substance that was reported as a suicide attempt. *T* tests, Pearson χ^2 tests, and Fisher exact tests were performed to evaluate characteristics associated with a history of OD.

Results: We examined the medical records of 200 patients (157 males and 43 females) with a mean ± SD age of 20.2 ± 2.8 years. At intake, 58 patients (29%) had a history of OD, and 62% of those patients had a history of unintentional OD only (n = 36). Youth with ≥ 2 SUDs were 3 times more likely to have a history of OD compared to youth with 1 SUD (all $P < .05$). Compared to those without a history of OD, those with an OD were more likely to be female and have lifetime histories of alcohol, cocaine, amphetamine, anxiety, depressive, and/or eating disorders (all $P < .05$).

Conclusions: High rates of OD exist in treatment-seeking youth with SUD. OD was associated with more SUDs and psychiatric comorbidity.

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[a]Pediatric Psychopharmacology Program, Division of Child Psychiatry, Massachusetts General Hospital, Boston, Massachusetts
[b]Addiction Recovery Management Service, Center for Addiction Medicine, Massachusetts General Hospital, Boston, Massachusetts
[c]Department of Psychiatry, Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts
**Corresponding author:* Amy M. Yule, MD, Addiction Recovery Management Services (ARMS), Massachusetts General Hospital, 151 Merrimac St, 6th Fl, Boston, MA 02114 (ayule@partners.org).

There has been a substantial increase in nonfatal and fatal overdoses (ODs) in the United States over the past 15 years.[1,2] In 2014, there were approximately 1.5 times more drug OD deaths in the United States than deaths from motor vehicle accidents.[2] Similar to general population trends, poisoning deaths among adolescents increased by 91% between 2000 and 2009.[3] Most ODs occur in individuals with substance use disorders (SUDs), and over half of individuals medically hospitalized in 2010 for an unintentional alcohol or drug poisoning had a SUD.[4]

A growing literature has identified risk factors associated with OD in adults, including nonmedical use of prescription opioids and heroin,[3,5–8] benzodiazepine use,[6,8] and history of OD.[9,10] Psychiatric risk factors associated with OD in substance users include depression[11] and increased impulsivity.[12] Likewise, a history of a suicide attempt has also been associated with history of OD in substance users,[5,13,14] although many of the studies that examined this relationship did not evaluate for differences related to the intentionality of the OD.[5,12,13]

To our knowledge, only 1 previous study has focused specifically on risk factors associated with a history of OD in youth with substance misuse. Silva and colleagues found that 24% of 596 urban youth 16 to 25 years of age with a history of nonmedical use of prescription opioids and/or tranquilizers had a lifetime history of OD involving prescription medication.[15] Substance-specific factors associated with an increased risk for OD included histories of being prescribed a tranquilizer, intranasal opioid use, injecting tranquilizers, and past-90-days injection drug use. Psychiatric symptoms and disorders were not assessed in the study; however, patients with a history of psychiatric hospitalization were at increased risk for OD. While informative, this community study of youth with prescription medication misuse may not generalize to SUD treatment-seeking youth, and psychiatric disorders were not systematically assessed.

Given the high rates of OD in young people, an increased knowledge of risk factors for OD in youth with SUD is critical to help focus screening and guide interventions directed at preventing OD. The main aims of this study were to examine the prevalence of OD and characterize substance and psychiatric risk factors associated with a history of OD among treatment-seeking youth with SUDs. Secondarily, we aimed to distinguish differences in the characteristics and correlates between unintentional and intentional OD in this sample. We hypothesized that more severe SUD would be associated with a history of OD. We also hypothesized that individuals with a history of a mood disorder and/or a psychiatric disorder associated with impulsivity, such as attention-deficit/hyperactivity disorder (ADHD), would be more

Clinical Points

- Despite a substantial increase in overdose among all age groups in the United States over the past 15 years, very little research has focused on overdose risk factors in youth with substance use disorders.
- Since overdose is common in treatment-seeking youth with substance use disorders, clinicians should carefully screen for overdose history and associated substance and psychiatric risk factors.

likely to have a history of OD compared to those without those respective disorders.

METHODS

We conducted a systematic retrospective medical chart review of consecutive intake assessments between January 2012 and June 2013 completed at the Addiction Recovery Management Service (ARMS), an outpatient SUD treatment program in a major northeast metropolitan medical center for youth 14 to 26 years of age.[16] Patients seen in the ARMS program had a semistructured assessment for SUD and psychiatric disorders including self-report of addiction severity (the Leeds Dependence Questionnaire [LDQ][17]) that were documented in standardized templates. The intake assessment was completed by a multidisciplinary team including master's-level social workers, psychologists, and psychiatrists with additional credentialing in addiction care. All cases were reviewed by the clinical and medical directors, who were both trained in child psychology and psychiatry with additional training and certification in addiction. For patients with more than 1 intake assessment during this time period, only the first initial intake assessment was included. Inclusion criteria included youth 16 to 26 years of age[18] at intake assessment who had a diagnosis of SUD (substance abuse or dependence, *DSM-IV-TR* criteria). Patient records were excluded if the patient did not meet criteria for SUD, was outside the inclusion age range, or had an incomplete record. Permission to conduct this study was obtained from the Partners Human Research Committee Institutional Review Board, which approved the study as providing adequate protection for human subjects.

Data extracted from patients' clinical records included demographics, characteristics of their substance use, lifetime SUD diagnoses, SUD treatment history, lifetime diagnoses of psychiatric disorders, psychiatric treatment history, OD history, and the type of substance ingested in the OD. Consistent with prior work,[9,19,20] unintentional OD was defined as substance use without intention of self-harm that was associated with significant impairment in level of consciousness. Intentional OD was defined as ingestion of any substance with the deliberate intention of self-harm[21] that was reported as a suicide attempt.

Statistical Analyses

Comparisons were made between patients with no history of OD and histories of OD, unintentional OD, and intentional OD. In the event of missing data, subjects were excluded only from those analyses of outcomes for which they were missing. Patients with a history of both unintentional and intentional OD were included in the intentional OD group for purposes of analysis. We analyzed continuous outcomes using Student independent *t* tests for parametric data and Wilcoxon rank sum tests for nonparametric data. Binary outcomes were analyzed using Pearson χ^2 tests or Fisher exact tests if any cell had an expected value less than 5. In the event of zero cells, we added 0.5 to all cells to calculate the odds ratio. We also performed stepwise logistic regression (backward selection, $P \geq .05$ for removal), starting with models that included all significant outcomes from the bivariate analyses to identify the best predictors of OD. All tests were 2-tailed and performed at the 0.05 α level using Stata, Version 14 (StataCorp LP, College Station, Texas). All data are presented as percentages, absolute numbers, or mean ± SD unless otherwise described.

RESULTS

The medical records for 243 consecutive initial intake assessments were examined. Forty-three records were excluded because they were outside the inclusionary age range (n = 21), a prior initial evaluation had already occurred outside the study timeframe (n = 12), the medical record was incomplete (n = 6), or the patient did not meet criteria for a SUD (n = 4). The full data set was available for 151 of 200 patients. Among the patients with missing information, 69.4% (n = 34) were missing only 1 data point.

Rates of OD

The lifetime prevalence of OD involving any substance was 29% (n = 58). Among patients with a history of OD, 62% (n = 36) had an unintentional OD only, 31% (n = 18) had an intentional OD only, and 7% (n = 4) had both unintentional and intentional OD. Among those with a history of OD, 41% (n = 24) had a history of more than 1 OD.

Demographics

We tested for demographic differences between patients with no history of OD and those with histories of OD, unintentional OD, and intentional OD (Table 1). Compared to patients without OD, those with a history of OD and intentional OD were more likely to be female (both $P \leq .001$). There was no significant difference in sex between patients with no history of OD and history of unintentional OD ($P > .05$). Furthermore, there were no significant differences between groups in race or mean age at initial evaluation.

Examining demographic differences between the unintentional and intentional OD groups revealed that those with a history of intentional OD were more likely to be female ($P = .009$). There were no differences between the unintentional and intentional OD groups in race or age at initial evaluation ($P > .05$). There was a nonsignificant trend that patients with history of intentional OD had their first OD at a younger age compared to those with a history of

Table 1. Demographic Characteristics of Subjects With No History of Overdose (OD) and History of OD Including Both Unintentional OD and Intentional OD

Characteristic	No OD (n = 142)	Any OD (n = 58)	Unintentional OD (n = 36)	Intentional OD (n = 22)
Age at initial evaluation, mean ± SD, y	20.0 ± 2.7	20.7 ± 2.9	20.6 ± 2.9	20.7 ± 2.9
Female gender, n (%)	21 (15)	22 (38)*	9 (25)	13 (59)*
Caucasian, n/n (%)[a]	126/138 (91)	51/56 (91)	31/34 (91)	20/22 (91)

[a]Full data set not available for race.
*$P \leq .001$ when compared to subjects with no history of OD.

Table 2. Substances Ingested in All Reported Overdoses (ODs) (n = 92)

Substance	Unintentional OD (n = 55), n (%)	Intentional OD (n = 37), n (%)	Test Statistic	*P* Value
Alcohol	28 (51)	7 (19)	$\chi^2 = 9.60$	.002
Opioids	15 (27)	6 (16)	$\chi^2 = 1.54$	.22
Cocaine	7 (13)	0	Fisher exact	.03
Benzodiazepines	6 (11)	6 (16)	$\chi^2 = 0.55$	.46
Over-the-counter medication	2 (4)	13 (35)	$\chi^2 = 16.1$	< .0001
Prescription medication[a]	1 (2)	10 (27)	Fisher exact	.0004
Other	2 (4)	0	Fisher exact	.51
Unknown	5 (9)	6 (16)	$\chi^2 = 1.07$	.30

[a]Does not include prescription opioids or benzodiazepines.

unintentional OD (17.3 ± 3.1 years vs 19.0 ± 2.8 years, $P = .06$). Age at first OD was unknown for 2 of the patients with intentional OD and 10 patients with unintentional OD.

Substances Ingested in OD

We evaluated for differences in the substances ingested in reported ODs between the unintentional and intentional groups (Table 2). Alcohol and cocaine were significantly more likely to be involved in unintentional ODs compared to intentional ODs (both $P < .05$). Over-the-counter and prescription medications were significantly more likely to be involved in intentional OD compared to unintentional OD (both $P < .05$).

OD Risk Relative to Number of SUD Diagnoses

We evaluated the risk for OD relative to the number of SUD diagnoses. Patients with 2 or more SUDs were approximately 3 times more likely to have a history of OD compared to patients with 1 SUD (2 SUDs: 37% vs 15%; OR = 3.19; 95% CI, 1.40–7.25; $P = .005$; 3 SUDs: 37% vs 15%; OR = 3.21; 95% CI, 1.20–8.57; $P = .02$; 4 SUDs: 37% vs 15%; OR = 3.28; 95% CI, 1.28–8.38; $P = .01$).

SUD and Psychiatric Characteristics Associated With OD

We examined if there were specific SUD and psychiatric characteristics linked to OD (Table 3). We found that a history of OD was associated with more severe addiction and higher rates of psychopathology. Those with a history of OD had more severe SUD as measured by the LDQ compared to those without a history of OD (11.0 ± 7.9 vs 8.6 ± 6.9; $z = 1.98$; $P = .05$). Information for the LDQ was not available for 3 patients. Those with a history of OD versus those without were more likely to have an alcohol, cocaine, or amphetamine use disorder (all $P \leq .01$). Those with a history of OD were also more likely to have histories of intravenous drug use, SUD-related medication-assisted treatment, and blackouts compared to those without a history of OD (all $P < .05$). Those with a history of OD also had higher rates of depressive, anxiety, and eating disorders (all $P < .05$) and were more likely to have histories of self-injurious behavior, suicide attempt, psychiatric hospitalization, and emotional, physical, or sexual abuse (all $P < .05$) compared to those without OD.

Results from our stepwise logistic regression identified histories of alcohol use disorder, eating disorder, blackouts, intravenous drug use, and psychiatric hospitalization as the best predictors of having a history of OD (all $P < .05$). Youth with these characteristics were 2 to 5 times more likely to have a history of OD.

Unintentional Versus Intentional OD

Examining only those patients with a history of OD, we tested for differences in SUD and psychiatric characteristics associated with unintentional versus intentional OD. While there were no differences in SUD variables between those with unintentional and intentional OD (all $P > .05$), those with an intentional OD had more severe psychopathology. Patients with an intentional OD compared to those with an unintentional OD were more likely to have a history of self-injurious behavior (73% vs 25%; OR = 8.00; 95% CI, 2.40– 26.7; $P < .001$) and prior inpatient treatment (82% vs 36%; OR = 7.96; 95% CI, 2.22–28.6; $P < .001$).

DISCUSSION

In a systematic retrospective review of consecutive intakes from an outpatient SUD treatment program, we found that 29% of youth aged 16 to 26 years had a history of OD. Our data support the hypothesis that OD is associated

Table 3. Bivariate Associations of Substance Use Disorder (SUD) and Psychiatric Characteristics Between Subjects With a History of Any Overdose (OD), Unintentional OD, and Intentional OD, Compared to Patients With No History of OD

Variable	Any OD (n = 58), OR (95% CI)	Unintentional OD (n = 36), OR (95% CI)	Intentional OD (n = 22), OR (95% CI)
Lifetime SUD diagnosis			
Alcohol	3.06 (1.49–6.26)**	2.39 (1.05–5.45)*	5.05 (1.42–17.84)**
Cannabis	0.60 (0.31–1.13)	0.49 (0.23–1.04)	0.84 (0.32–2.21)
Opioid	1.22 (0.65–2.28)	1.38 (0.66–2.90)	0.99 (0.39–2.52)
Cocaine	2.75 (1.25–6.02)**	2.24 (0.75–6.23)	3.64 (1.09–11.36)*
Benzodiazepine	1.99 (0.79–5.02)	2.16 (0.61–6.83)	1.70 (0.28–7.17)
Amphetamine	2.87 (1.24–6.64)**	2.81 (0.92–8.17)*	2.89 (0.72–10.11)
SUD characteristics (history of)			
Abstinence[a]	2.88 (0.82–10.19)	5.73 (0.85–247)	1.44 (0.30–13.85)
Intravenous drug use	2.26 (1.06–4.83)*	2.85 (1.21–6.72)**	1.44 (0.32–5.05)
Inpatient detoxification	1.62 (0.80–3.24)	1.71 (0.76–3.89)	1.46 (0.43–4.37)
Medication-assisted treatment	2.40 (1.11–5.18)*	1.97 (0.78–4.98)	3.18 (0.96–9.78)
Withdrawal symptoms[a]	1.48 (0.77–2.86)	1.47 (0.68–3.20)	1.50 (0.55–4.11)
Blackouts[a]	3.22 (1.46–7.13)**	3.79 (1.38–10.37)**	2.52 (0.80–7.96)
Lifetime psychiatric diagnosis			
Attention-deficit/hyperactivity disorder	0.79 (0.43–1.47)	0.86 (0.41–1.80)	0.69 (0.28–1.70)
Anxiety disorder	2.11 (1.11–4.00)*	1.82 (0.85–3.87)	2.74 (1.01–7.41)*
Depressive disorder	2.38 (1.28–4.44)**	1.88 (0.90–3.92)	3.60 (1.38–9.39)**
Bipolar disorder	1.46 (0.58–3.70)	1.14 (0.26–3.97)	2.02 (0.44–7.44)
Mood disorder (not otherwise specified)	1.01 (0.39–2.58)	1.18 (0.32–3.70)	0.74 (0.08–3.51)
Psychosis	0.34 (0.01–2.74)	0.25 (0.01–4.44)	0.92 (0.02–7.77)
Eating disorder	5.65 (1.66–22.2)**	5.41 (1.28–24.00)**	5.98 (1.08–30.74)*
Psychiatric characteristics (history of)			
Self-injurious behavior	2.50 (1.31–4.79)**	1.10 (0.47–2.57)	8.81 (3.19–24.33)***
Suicide attempt[a]	11.3 (4.66–27.54)***	0.49 (0.01–3.90)	712 (39.9–12,773)***
Psychiatric medication[a]	2.28 (0.89–5.84)	1.32 (0.50–3.47)	12.0 (0.71–204)
Mental health treatment	2.08 (0.68–6.42)	1.23 (0.37–5.34)	7.11 (0.41–121)
Psychiatric hospitalization	3.14 (1.66–5.93)**	1.55 (0.71–3.36)	12.3 (3.92–38.7)***
Abuse (emotional, physical, and/or sexual)[a]	2.36 (1.21–4.57)**	1.60 (0.70–3.62)	4.18 (1.65–10.59)***

[a]Sample sizes for variables with missing information: abstinence, 185; withdrawal symptoms, 184; blackouts, 192; suicide attempt, 199; psychiatric medication, 197; abuse, 196.
*$P < .05$.
**$P \leq .01$.
***$P \leq .001$.
Abbreviations: CI = confidence interval, OR = odds ratio.

with more severe SUD and psychopathology. OD risk was directly related to the number of SUD diagnoses. Our findings of specific drug- and psychopathology-related risk factors partially support our hypothesis—whereas alcohol, cocaine, and amphetamine use disorders were associated with OD, no meaningful associations were found with opioid or benzodiazepine use disorders. Similarly, while depressive, anxiety, and eating disorders were associated with OD, no associations were observed with ADHD or other impulse-related psychopathology. Individuals with intentional OD had more severe psychopathology than those with unintentional OD. These data suggest the need to carefully screen for OD and associated risk factors during intake assessment for SUD.

The prevalence of lifetime history of OD in our sample (29%) was reminiscent of the prevalence of lifetime history of OD in 2 other studies with similar mean sample ages (21 and 21.5 years of age).[15,22] The marginal differences in prevalence may have been related to the study population sampled. Silva and colleagues[15] may have found a lower prevalence of OD (23%) since they queried youth only about OD due to prescription opioids and/or tranquilizers. It is less likely that our inclusion of intentional OD as part of the assessment of prevalence of OD contributed to differences in prevalence with the Silva and colleagues sample since they did not assess intentionality when querying youth about their OD history. Mills and colleagues[22] may have found a higher prevalence of OD (41%) because all participants were presenting for treatment for heroin dependence and the majority had a history of intravenous use. Independent of these differences, overall, our retrospective analysis and the broader literature suggest that OD is a common phenomenon among treatment-seeking youth. More research is needed to assess the incidence and mitigation of OD risk in youth longitudinally.

The 3-fold increased risk for OD associated with patients who have more than 1 SUD is noteworthy and suggests that the number of SUD diagnoses may be a marker of SUD severity that is meaningful in the assessment of OD risk. Our results support findings by Bohnert and colleagues,[13] who found that adults seeking treatment for the use of 2 or more substances had an increased risk for a history of OD and a history of having both an OD and a suicide attempt. More research is needed to clarify if the increased risk for OD associated with more than 1 SUD is related to polysubstance use or SUD severity.

In general, we found that youth with alcohol, cocaine, or amphetamine use disorders as well as those with more severe SUD were at increased risk for OD. Alcohol and cocaine have been identified as risk factors for OD in several studies. Among patients with intravenous substance use, alcohol use,[6,9,23] binge drinking,[24,25] cocaine use,[9] and intravenous use of cocaine[6,19,24] were associated with increased risk for OD. Interestingly, the risk for OD associated with amphetamine use has been less commonly examined, but regular use of amphetamines has been previously identified as a risk factor for OD in patients seeking SUD treatment.[26,27]

The association found between depressive disorders and a history of OD, and in particular, intentional OD in youth, is consistent with previous literature in adults linking elevated risk for OD with major depression.[11] Our findings of an association between anxiety disorders and a history of OD and intentional OD are similar to work by Maloney and colleagues[12] in adults with opioid use disorders. They found that anxiety disorders were linked with a history of suicide attempt but not with unintentional OD.[12] Maloney and colleagues also reported an association between impulsivity and unintentional OD, which was a finding hypothesized but not found in our current study. Our findings may have differed because we did not evaluate symptoms of impulsivity at initial evaluation and assessed only for a lifetime history of impulsivity-related psychopathology. Our findings coupled with the existing literature support the importance of assessing for depressive and anxiety disorders when assessing OD risk.

Although limited by small sample size, our results linking eating disorders with all types of OD and the identification of eating disorder as the most significant predictor of OD are novel but not surprising findings. SUDs commonly co-occur with eating disorders,[28] with one report highlighting drug-related OD to be the most common method of suicide attempt among a sample of women referred for outpatient eating disorder treatment.[29] If replicated, it would be helpful to identify the mechanism linking OD and eating disorders in youth.

We found intriguing differences between those with intentional and unintentional ODs. Youth with a history of intentional OD had more severe psychopathology and a younger age at first OD than those with unintentional OD. Interestingly, there were no significant differences in SUD diagnoses or SUD characteristics between the groups. These findings are similar to work by Best and colleagues,[30] who in a sample of adults receiving methadone maintenance, reported no difference in heroin use among those with and without intentional OD. Those with intentional OD, however, endorsed greater symptoms of psychopathology, increased depressive symptoms, relative to those with unintentional OD.[30]

Although not an a priori hypothesis, we did examine for sex differences and found that females were more likely to have a history of OD and more intentionality associated with the OD compared to males. Our findings are similar to others[6] who found that women were at increased risk to have a history of OD. In contrast, Pabayo and colleagues[24] did not find a difference in the prevalence of OD between adult men and women but did find that women, but not men, with several sources of social support were significantly less likely to have a history of OD at baseline and through follow-up. More work is needed to examine sex differences in risk for OD with particular attention to intentionality and age.

There are several methodological limitations of our study that are important to consider when making any generalizations from the findings. Our data were derived retrospectively in a systematic review of consecutive medical records. We relied on patient report regarding substances involved in past overdoses and did not have detailed information on the type of alcohol or opioid used or toxicology reports for collateral information. For alcohol and opioids, use of higher alcohol content products and higher potency opioids such as fentanyl may be important mediators of overdose risk. This study also lacked more detailed information regarding suicidal behavior since there was no standardized assessment of suicidality. It is possible that an OD classified as unintentional and not identified as a suicide attempt may have involved passive thoughts of death. Furthermore, our data were also derived from treatment-seeking youth and may not generalize to youth not seeking treatment. We describe a heterogeneous sample, and some of the cell sizes were small, limiting our power. Since our sample was mostly Caucasian, the findings may not generalize to other ethnic groups.

Despite these limitations, our findings from treatment-seeking youth with SUD suggest that OD is common and begins relatively early. Youth with more lifetime SUD diagnoses and psychopathology are at increased risk for OD. Amid the opioid epidemic, clinicians who work with youth need to assess for other substances such as alcohol and stimulants that were found to be associated with increased risk for OD. Similarly, it seems parsimonious to assess for psychiatric risk factors when determining OD risk in SUD youth. Future studies should also examine the effect of treatment longitudinally in mitigating the risk for subsequent OD with frequent follow-up to capture more details regarding substances used and psychiatric symptoms at or around the time of overdose.

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Co-Director of the Center for Addiction Medicine at Massachusetts General Hospital. **Mr Carrellas**, **Ms Fitzgerald**, and **Drs McKowen**, **Nargiso**, **Bergman**, and **Kelly** have nothing to disclose.

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