

Benzodiazepine and Stimulant Prescriptions Before Overdose in Youth

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In 2019, 4777 youth died of a drug overdose in the United States.¹ Seven-hundred and twenty-seven youth died of overdoses involving benzodiazepines (BZDs) and 902 from overdoses involving psychostimulants.² Opioid-related overdose deaths frequently involve other substances, and in youth, stimulants and BZDs are the most commonly involved substances.³ Overdoses can involve prescription drugs accessed through medical prescriptions or through illicit means. Among persons aged 18 to 25 years, 5.8% report past-year prescription stimulant misuse and 3.8% prescription BZD misuse.⁴

To inform overdose prevention efforts, we determined how often youth with medically treated overdoses involving BZDs and stimulants had recent BZD or stimulant prescriptions.

METHODS

We included youth (15–24 years) from the MarketScan commercial claims database who experienced an overdose involving stimulants or BZDs (January 01, 2016 to December 31, 2018). MarketScan covers privately insured individuals and captures diagnoses and procedures from inpatient and outpatient visits and dispensed prescriptions.⁵ Overdose events treated in an emergency department (ED) or inpatient setting were included, defined using *International*

Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes for an unintentional, intentional, or undetermined poisoning initial encounter (Table 1). Stimulant overdoses were limited to overdoses involving amphetamine or methylphenidate. We selected the first overdose per person and required ≥ 6 months of insurance enrollment with prescription coverage before the overdose.

In the 6 months before the overdose, we identified dispensed BZD and stimulant prescriptions and mental health diagnoses (Tables 1 and 2). We summed the number of fills and days' supply for prescriptions dispensed in the 6 months before the overdose. Results were stratified by intentional self-harm versus unintentional overdoses. In a secondary analysis, class of prescription stimulant was considered with whether the overdose involved amphetamine or methylphenidate.

RESULTS

We identified 2986 youth who experienced an overdose involving BZDs and 971 youth with an overdose involving stimulants (amphetamine or methylphenidate). The majority of youth had a previous mental health diagnosis; 56% of overdoses involving BZDs were intentional compared to 40% of overdoses involving stimulants (Table 1).

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TABLE 1 Previous Prescriptions in Youth (15–24 y) With a Medically-Treated Overdose Involving a BZD, 2016–2018

Overdoses Involving BZDs	N = 2986	Intent of Overdoses Involving BZDs ^a		P
		Intentional (n = 1664)	Unintentional (n = 1160)	
Age at overdose, y, median (IQR)	20 (17–22)	20 (18–22)	20 (18–22)	
Female, n (%)	1556 (52.1)	1045 (62.8)	447 (38.5)	<.001
Mental health diagnosis in previous 6 mo, ^b n (%)	2232 (74.7)	1300 (78.1)	813 (70.1)	<.001
Previous BZD prescription, ^c n (%)				
0–1 mo	854 (28.6)	590 (35.5)	234 (20.2)	<.001
0–6 mo	1243 (41.6)	850 (51.1)	348 (30.0)	<.001
Days from overdose to most recent prescription, median (IQR)	16 (5–39)	16 (5–37)	15 (4–40)	
Subset with BZD prescription(s) in previous 6 mo	N = 1243	n = 850	n = 348	
Number of BZD fills, median (IQR)	3 (1–5)	2 (1–4)	3 (1–5)	
>3 fills dispensed, n (%)	470 (37.8)	300 (35.3)	156 (44.8)	.002
Total BZD d supplied, median (IQR)	60 (30–120)	60 (30–120)	73 (30–136)	
>90 d dispensed, n (%)	413 (33.2)	267 (31.4)	134 (38.5)	.018
Mental health diagnosis in previous 6 mo, ^b n (%)	1153 (92.8)	785 (92.4)	324 (93.1)	.653

ICD-10-CM overdose definitions: overdose involving BZD: T42.4 × 1A, T42.4 × 2A, T42.4 × 4A. Previous BZD prescriptions identified through records of dispensed prescriptions before overdose event: alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, lorazepam, midazolam, oxazepam, quazepam, temazepam, triazolam. BZD, benzodiazepine; IQR: interquartile range.

^a Undetermined overdose events not displayed (N = 162); if multiple overdose codes were recorded with differing intents (intentional, unintentional, undetermined), precedence in classification was given to intentional then unintentional.

^b Mental health diagnoses identified in 6 mo before overdose event (excluding date of overdose event): International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM: 290–319; ICD-10-CM: F01–F99; see Supplemental Table 3 for specific diagnoses.

^c Prescription anytime in previous 0 to 12 mo: overall: 1380 (46.2%), intentional: 923 (55.5%), unintentional: 407 (35.1%).

Twenty-nine percent of youth with overdoses involving BZDs had a prescription BZD dispensed in the previous 30 days and 42% in the previous 6 months (Table 1, Fig 1). Among youth with a BZD prescription in the previous 6 months, 33% received >90 days' supply, and 73% had an anxiety disorder diagnosis (Supplemental

Table 3). Youth with intentional BZD overdoses were more likely to have a recent BZD prescription (51%) than those with unintentional overdoses (30%).

A quarter of youth with an overdose involving stimulants (amphetamine/methylphenidate) had a stimulant prescription dispensed in the

previous 30 days and 39% in the previous 6 months (Table 2, Fig 1). Among youth with a stimulant prescription in the previous 6 months, 56% received >90 days' supply and 71% had an ADHD diagnosis (Supplemental Table 4). Youth with intentional stimulant overdoses were more likely to have a recent stimulant prescription

TABLE 2 Previous Prescriptions in Youth (15–24 y) With a Medically-Treated Overdose Involving a Stimulant, 2016–2018

Overdoses Involving Stimulants (Amphetamine or Methylphenidate)	N = 971	Intent of Overdoses Involving Stimulants ^a		P
		Intentional (n = 388)	Unintentional (n = 524)	
Age at overdose, y, median (IQR)	19 (17–22)	18 (16–20)	20 (18–22)	
Female, n (%)	415 (42.7)	213 (54.9)	179 (34.2)	<.001
Mental health diagnosis in previous 6 mo, n (%) ^b	634 (65.3)	299 (77.1)	299 (57.1)	<.001
Previous stimulant prescription, ^c n (%)				
0–1 mo	239 (24.6)	137 (35.3)	93 (17.7)	<.001
0–6 mo	380 (39.1) ^d	219 (56.4)	147 (28.1)	<.001
Days from overdose to most recent prescription, median (IQR)	20 (8–47)	21 (9–47)	14 (5–46)	
Subset with stimulant prescription in previous 6 mo	N = 380	n = 219	n = 147	
Number of stimulant fills, median (IQR)	4 (2–5)	3 (2–5)	4 (2–6)	
>3 fills dispensed, n (%)	191 (50.3)	102 (46.6)	83 (56.5)	.064
Total stimulant days supplied, median (IQR)	120 (60–180)	117 (60–150)	120 (90–180)	
>90 d dispensed, n (%)	213 (56.1)	112 (51.1)	95 (64.6)	.011
Mental health diagnosis in previous 6 mo, n (%)	335 (88.2)	199 (90.9)	123 (83.7)	.038

ICD-10-CM overdose definitions: overdose involving stimulant: amphetamine (T43.621A, T43.622A, T43.624A) and methylphenidate (T43.631A, T43.632A, T43.634A). Previous stimulant prescriptions identified through records of dispensed prescriptions before overdose event: amphetamines (amphetamine, dextroamphetamine, lisdexamfetamine, methamphetamine) and methylphenidates (methylphenidate, dexmethylphenidate). Mental health diagnoses identified in 6 mo before overdose event (excluding date of overdose event): International Classification of Diseases, 9th and 10th Revisions, Clinical Modification (ICD-9-CM): 290–319; ICD-10-CM: F01–F99; see Supplemental Table 4 for specific diagnoses. IQR, interquartile range.

^a Undetermined overdose events not displayed (N = 59); if multiple overdose codes were recorded with differing intents (intentional, unintentional, undetermined), precedence in classification was given to intentional then unintentional.

^b Mental health diagnoses identified in 6 mo before overdose event (excluding date of overdose event): ICD-9-CM: 290–319; ICD-10-CM: F01–F99; see Supplemental Table 4 for specific diagnoses.

^c Prescription anytime in previous 0 to 12 mo: overall: 416 (42.8%), intentional: 238 (61.3%), unintentional: 162 (30.9%).

^d Overdose by type: overdose involving amphetamine (n = 833), 31.8% have amphetamine prescription in previous 6 mo; overdose involving methylphenidate (n = 146), 64.4% have methylphenidate prescription in previous 6 mo.

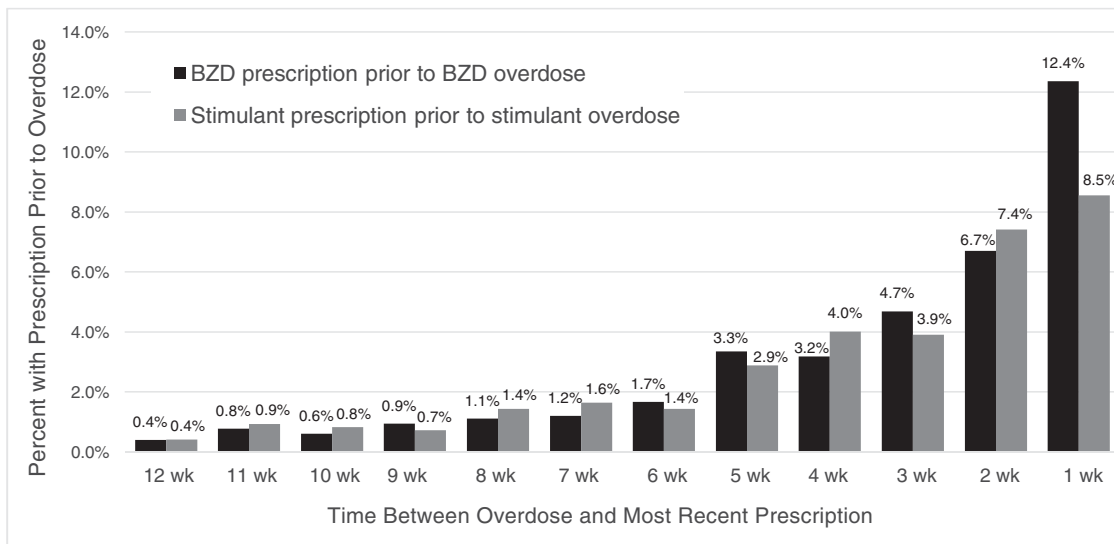


FIGURE 1

Proportion of youth (15–24 years) with a prescription fill* before an overdose involving a benzodiazepine or stimulant by time between prescription and overdose. BZD, benzodiazepine. *Percent with BZD prescription before an overdose involving a BZD; percent with stimulant prescription before an overdose involving amphetamine or methylphenidate.

(56%) than those with unintentional overdoses (28%).

DISCUSSION

A considerable fraction of youth with overdoses involving BZDs and stimulants had recent prescriptions for these drugs. Previous BZD and stimulant prescriptions were more common in youth with intentional overdoses. This underscores the importance of incorporating self-injury assessment into clinical practice for youth prescribed BZDs and stimulants and highlights the need for differing prevention efforts for intentional and unintentional youth overdoses.

The majority of youth who received a BZD or stimulant prescription before overdose had a mental health diagnosis. These medications are prescribed for mental health problems common in youth^{6,7} and can be effective treatments. However, because these drugs are commonly misused⁴ and involved in overdoses, weighing risks and

benefits when prescribing them remains imperative.

Primary considerations of this research include that we cannot distinguish amphetamine overdoses related to prescription amphetamine versus an illicit substance. We miss overdoses that did not present to the ED or hospital, including fatal overdoses occurring outside these settings, and events in which BZD or stimulant involvement was not recorded. Without comparator groups, we are unable to assess comparative overdose liability by prescription characteristics.

Given that one-fourth of youth who overdose on these drugs receive prescriptions for them in the previous month, results suggest an avenue of prevention and motivate future work examining overdose risk after prescription. Because the potential for harm with BZD and stimulants increases with selected combinations of prescription medications, alcohol, and illicit drugs, and especially concurrent BZD and opioid use,^{8,9} these

concerns warrant attention and discussion at prescription initiation.

ABBREVIATIONS

BZD: benzodiazepine
 ED: emergency department
 IQR: interquartile range
 ICD-9-CM: *International Classification of Diseases, Ninth Revision, Clinical Modification*
 ICD-10-CM: *International Classification of Diseases, Tenth Revision, Clinical Modification*

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