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# INTERMITTENT EXPLOSIVE DISORDER AND SUBSTANCE USE DISORDER: ANALYSIS OF THE NATIONAL COMORBITY STUDY - REPLICATION SAMPLE

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#### **Abstract**

**Objective.**—A relationship between aggression and substance use has been debated for many years. While substance use increases the risk of aggressive behavior, no studies have reported on the relationship between impulsive aggression and substance use/disorder, specifically.

**Methods.**—We analyzed data from the community-based National Comorbidity Study-Replication (n = 9,282 subjects) in order to examine the relationship between current DSM-5 Intermittent Explosive Disorder (IED), a disorder of impulsive aggression, and current substance use disorders (SUD), overall, and with regard to alcohol, tobacco, and cannabis use disorder and non-disordered use.

**Results.**—Occurrence of current SUD was elevated in current IED  $\underline{vs}$ . Non-IED adult subjects and onset of IED preceded that for SUD in 92.5% of comorbid IED+SUD cases. This relationship was not due to the presence, or absence, of current depressive or anxiety disorders. Examination of the severity of IED and of SUD revealed that the presence of IED increases SUD severity but that the presence of SUD does not increase IED severity.

**Conclusion.**—Subjects with IED are at increased risk of developing substance use disorder, compared with those without IED. This suggests that history of recurrent, problematic, impulsive aggression is a risk factor for the later development of SUD rather than the reverse. If so, effective treatment of impulsive aggression, before the onset of substance misuse, may prevent, or delay, the development of SUD in young people.

#### Keywords

IED SUD; Impulsive Agg	ression	

#### INTRODUCTION

Intermittent Explosive Disorder (IED), as defined in DSM-5, is characterized by recurrent, problematic, impulsive aggressive behavior<sup>1</sup>. Aggression in IED may be displayed as high

frequency/low intensity aggression that is non-destructive or injurious, or as low frequency/high intensity aggression that is destructive and/or injurious<sup>2</sup>. However manifest, aggression in IED is impulsive, and/or anger-based. Based on data analyzed for the DSM-5 Task Force, about 70% of individuals with IED display both forms of impulsive aggression, 20% display only the high frequency/low intensity aggression, and 10% display only the low frequency/high intensity aggression<sup>3</sup>. Aggressive behavior in IED is most often provoked in social interactions. In IED, hostile cognitive distortions lead to misinterpretations of non-threatening social-emotional cues as threatening and an inappropriately aggressive response<sup>4</sup>.

Initially it was thought that the impulsive aggressive behavior in IED was due to the presence of other psychiatric disorders<sup>5</sup>. However, epidemiologic data indicate that the age of onset of IED is earlier than that of most other psychiatric disorders<sup>6,7</sup>. Accordingly, when impulsive aggressive outbursts are not limited to episodes of another disorder, the diagnosis of IED may be made<sup>1</sup>. In the clinic, IED is often co-morbid with other disorders such as depressive, anxiety, and substance use, disorders<sup>8,9</sup>. We have reported on the comorbidity of IED with depressive and anxiety disorders, previously<sup>2</sup>, but have not reported on comorbidity of IED with substance use, or substance use disorders.

A relationship between aggression and substance use disorders, has been discussed in the literature for many years. In general, substance use increases the risk of aggressive behavior <sup>10-12</sup>. Notably, alcohol, cocaine, amphetamines, and cannabis have been found to increase the risk for aggressive behavior in human subjects. This statement belies the complexity of such comorbidity and there are important issues regarding how aggression and how substance use is defined. For example, there are at least two forms of aggressive behavior: a) aggressive behavior that is impulsive or reactive/defensive in nature <sup>13-15</sup>; b) premeditated aggressive behavior, typically associated with psychopathy <sup>13,16</sup>. There are also several ways in which substances may influence aggressive behavior. Firstly, through acute substance intoxication; secondly, through substance withdrawal; and thirdly, through its association with environments steeped in violence <sup>11</sup>.

With the advent of a reliable, and valid, clinical entity of impulsive aggression (IED)<sup>1</sup>, it is timely to examine the relationship between IED and substance use (SU) and substance use disorder (SUD). In this study, we reanalyzed data from the National Comorbidity Study-Replication (NCS-R)<sup>17</sup> project in order to examine the relationship between current IED and current SUD. Based on the literature, and on our experience in working with individuals with recurrent, problematic, impulsive aggressive behavior, we hypothesized that: a) risk of current SUD would be significantly increased in current IED, compared with Non-IED, subjects; b) in cases of current IED+SUD comorbidity, age of onset of IED would precede that for SUD; c) IED+SUD comorbidity would not be influenced by current comorbid depressive or anxiety disorder; d) among SUDs, risk of alcohol, tobacco, and cannabis use disorders would each be elevated in IED, compared with Non-IED, subjects; and, e) a "dose (or use frequency) effect" would be observed on the risk of specific SUDs in IED <u>vs.</u> Non-IED subjects.

#### **METHODS**

#### Subjects.

The NCS-R sample used in this analysis had 9,282 subjects. Details regarding the design and acquisition of these data have been previously published<sup>17</sup>. This study was approved by our Committee for the Protection of Human Subjects (IRB).

#### Assignment of Diagnoses.

The NCS-R study was designed to assign DSM-IV diagnoses. However, raw NCS-R data allow DSM-IV diagnoses to be updated to those of the DSM-5<sup>1</sup>. For the diagnosis of current IED, subjects reported at least three "anger attacks" in any given year with at least one in the past year (Criteria A2). In addition, "anger attacks" were out of proportion to the circumstances in which they occurred (Criteria B), impulsive in nature (Criteria C), associated with functional impairment and/or distress (Criteria D) with "anger attacks" occurring in the absence of other psychiatric disorders (Criteria F); all subjects were greater than the age of 6 (Criterion E). Subjects meeting the DSM-IV criteria for drug/alcohol abuse or dependence were assigned a diagnosis of DSM-5 Substance Use Disorder (SUD) when at least two of the DSM-5 SUD criteria were met. Data were available for alcohol, tobacco, cannabis, and cocaine, but not for other substances of abuse. Characteristics of the sample are listed in Table I.

#### Focus of Study and Severity of IED, SUD, and Substance Use.

We focused on the current disorders of subjects in the sample because it was clear when these disorders were comorbid and because these data were less likely to have retrospective bias compared with lifetime disorders. There were sufficient numbers of subjects with current IED and current alcohol, tobacco, or cannabis use disorders. However, only one subject with current IED had current cocaine use disorder and, thus, similar analyses could not be performed for this substance use disorder. Severity of IED was assessed by maximum number of "anger attacks" in any year; severity of SUD was assessed by mean number of DSM-5 criteria met for SUD. Current substance use was assessed by four levels of weekly use: "minimal", "low", "medium", and "high". These levels were defined as follows: Alcohol: less than one, 1-6, 7-14, and greater than 14 drinks per week; Tobacco: less than 10, 10-20, 21-40, and greater than 40 cigarettes per day; Cannabis: less than one time, 1-2 times, 3-4 times, and 5-7 times weekly.

#### Statistical Analysis.

Statistical procedures included Chi-square, Fisher Exact Test (FET), binary logistic regression, analysis of covariance (ANCOVA), and paired t-test, as appropriate. All reported odds ratios were adjusted for age, sex, ethnicity, education, and marital status. A two-tailed alpha value of 0.05 was used to denote statistical significance for all analyses.

#### **RESULTS**

#### Comorbidity of Current IED and Current SUD.

Despite prevalence of current SUD of 5.7% (532/9282), and of current IED of 2.2% (207/9282), comorbidity of current SUD in current IED subjects was significantly greater than chance compared with Non-IED subjects [28.5% (59/207)  $\underline{vs}$ . 5.2% (473/9075); Odds Ratio: 5.42 (95% CI: 3.88-7.55), p < .001].

#### Current IED and SUD Comorbidity: Age of Onset of IED and SUD.

Onset of IED preceded onset of SUD in 91.5% (54/59) of current IED+SUD comorbid subjects. In IED+SUD subjects for whom IED preceded SUD, onset of IED preceded that of SUD by more than eight years (8.3  $\pm$  6.9; i.e., age 11.9  $\pm$  4.1 for IED  $\underline{\textit{vs}}$ . age 20.2  $\pm$  6.8 years for SUD, paired  $t_{53}$ = 8.80, p < .001) with a range of 1-32 years and a median of 6.5 years. In the remaining five IED+SUD subjects, onset of SUD preceded that of IED by less than one year (0.6  $\pm$  0.6; i.e., age 17.0  $\pm$  3.1 for SUD vs. age 17.6  $\pm$  2.6 years for IED, paired  $t_4$  = 2.45, p = .07) with a range of 0 to 1 year and a median of 0.5 years. For all IED (n = 320) and SUD (n = 532) subjects, respectively, mean ages of onset were 13.2  $\pm$  6.8 and 21.0  $\pm$  9.0 years (t<sub>850</sub> = 13.38, p < .001).

#### Current IED and SUD Comorbidity: Severity of IED and SUD.

ANCOVA revealed that IED and IED+SUD subjects were similar in IED severity, and significantly higher in IED severity compared with SUD (and Non-IED) subjects; figure 1, left. Conversely, IED+SUD subjects were significantly higher in SUD severity compared with SUD and IED (and Non-IED) subjects; figure 1, right.

#### Comorbid IED and SUD as a Function of Depressive and Anxiety Disorders (Table II).

To explore if relationships between current IED and current SUD extend to other disorders often comorbid with IED<sup>8,9</sup>, we performed similar analyses with current depressive disorder (DEP) and with current anxiety disorder (ANX). Current IED was more prevalent among current SUD in subjects regardless of current DEP or current ANX. For both the DEP and ANX comparisons, however, significantly greater odds ratios of SUD in IED subjects were observed in subjects without ANX compared to subjects with ANX.

## Comorbid IED with Specific SUDs: Alcohol Use Disorder (AUD), Tobacco Use Disorder (TUD), and Cannabis Use Disorder (CUD).

Frequency of current IED with each of these current SUD disorders was elevated compared with Non-IED subjects as follows: AUD [15.5% (32/207)  $\underline{vs}$ . 2.1% (188/9075): Odds Ratio: 5.78 (95% CI: 3.79–8.85), p < .001]; TUD [13.5% (28/207)  $\underline{vs}$ . 3.1% (283/9075): Odds Ratio: 4.06 (95% CI: 2.656.24), p < .001]; CUD [7.2% (15/207)  $\underline{vs}$ . 0.6% (52/9075): Odds Ratio: 6.65 (95% CI: 3.58-12.35), p < .001], Differences in these odds ratios were not statistically significant: AUD and TUD (z = 1.08, p = .280); AUD and CUD (z = 0.43, p = .668); CUD and TUD (z = 1.50, p = .134). As with SUD overall, age of onset of IED in current AUD, TUD, or CUD subjects was lower than that for the age of onset for AUD (11.7

 $\pm$  4.1 <u>vs.</u> 19.1  $\pm$ 5.8,  $t_{31}$  = 7.26, p < .001), TUD (11.9  $\pm$  4.3 vs. 22.9  $\pm$  6.7,  $t_{27}$ = 7.24, p < .001), or CUD (12.4  $\pm$  3.0 vs. 14.1  $\pm$ 2.2,  $t_{14}$  = 2.19, p < .05).

#### Severity of IED and Current Frequency of Alcohol, Tobacco, and Cannabis Use.

In order to determine if these observations held true across different levels of substance use, we examined the relationship of IED severity with weekly current substance use defined as "minimal", "low", "medium", and "high". Compared with minimal use, significant differences in IED severity were observed at "high use" for alcohol and cannabis and for "medium use" level for tobacco (fig. 2). However, even at the high current use of alcohol and cannabis, less than a third of these subjects met DSM-5 criteria for current AUD (28.8%) or current CUD (32.2%), respectively, and less that 20% met criteria for TUD at the moderate current use of tobacco (18.8%), indicating that these relationships are not firmly defined by DSM-5 criteria for SUD.

## Current IED and Tobacco and Cannabis Use Disorder as a Function of Alcohol Use Disorder.

Since current AUD was significantly comorbid with current TUD [Odds Ratio: 5.13 (95% CI: 3.47-7.58); p < .001] and with current CUD [Odds Ratio: 27.25 (95% CI: 15.88-46.74); p < .001], it was of interest to determine if the presence of current AUD influenced comorbidity with current IED. Similar to the results above, an elevated odds ratio for current TUD was observed in current IED  $\underline{vs}$ . Non-IED but only in subjects without current AUD; Table III, left. For current CUD, an elevated odds ratio for IED was observed regardless of current AUD, though the odds ratio for subjects without current AUD was significantly greater than that for those with current AUD; Table III, right.

#### DISCUSSION

The primary finding in this analysis is that current IED, a categorical expression of impulsive aggression, is comorbid with current SUD and represents an overall risk for SUD that may be five-fold greater than that observed in Non-IED subjects. In addition, we found that the age of onset of IED was earlier than that for SUD for the vast majority of IED+SUD comorbid subjects. This finding in a population-based sample of adults supports a previous report that the onset of IED precedes SUD in adolescents<sup>7</sup>. Thus, IED may identify a risk factor for the development of maladaptive substance use, and use disorder, in later adolescence *and* adulthood<sup>15</sup>.

Examination of the comparative severity of IED and SUD in IED+SUD subjects suggests an effect of IED on SUD rather than the reverse. Specifically, we found that comorbid IED +SUD was associated with greater SUD severity (compared with SUD only subjects) in the absence of any difference in IED severity (compared with IED only subjects). In addition, SUD severity in IED only subjects was significantly greater than that for Non-IED/Non-SUD subjects suggesting that the even the presence of IED alone increases the risk of substance use disorder symptoms. It is possible that IED is an early indicator of a more severe impulsive externalizing liability that expresses in later substance use.

Another notable observation is the influence of current comorbidity of depressive and anxiety disorders in its association of IED and SUD. In this study, odds ratios for subjects with, or without, current depressive or anxiety disorders were each greater than chance, though to different degrees. Specifically, the risk of IED+SUD in subjects with current anxiety (but not depressive) disorder was lower than that for subjects without current anxiety disorder by about five-fold. This is because the presence of current depressive disorder increased IED+SUD comorbidity more so than the presence of current anxiety disorder. The reason for this is unknown, as depressive and anxiety disorders are highly comorbid with each other and both are known to be associated with behavioral irritability. However, these data are unable to shed any further light on this observation.

The NCS-R data set did not allow an analysis of all possible substance use disorders and we were only able to examine SUDs related to alcohol, tobacco, and cannabis. For these substances, current IED was associated with a four- to a nearly seven-fold increased risk for current AUD, TUD, and CUD, though these risk estimates did not significantly differ from each other.

Examination of the association between current IED and the individual substances investigated revealed a significant difference in IED severity between "minimal" and "highest" use levels for alcohol and cannabis; a similar difference was observed at the "medium" use level for tobacco. This approach complements that of the DSM categorical approach and suggests, further, that IED is associated with increases subclinical use of these substances.

While these data cannot provide definitive insight on the direction of these relationships, these data are consistent with other relevant data. For example, human laboratory studies demonstrate that alcohol administration increases aggression particularly in individuals with higher scores on aggression measures compared with individuals with lower scores on these measures<sup>18</sup>. Similar interpretations for the relationship between aggression and tobacco use and cannabis use, however, are not likely as straightforward. Specifically, the possibility that increasing use of cannabis leads to increasing impulsive aggressive behavior is just as plausible as the possibility that increasing levels of aggressive behavior lead to greater cannabis use. While studies in this area are few, acute administration of cannabis has been shown to reduce aggressive responding in some <sup>19</sup>, though not all <sup>20</sup>, laboratory aggression tasks. Conversely, it is also known that irritability and aggressive behavior can emerge during cannabis withdrawal within 1-5 days of the absence of further cannabis intake<sup>21-24</sup>. Thus, it is unknown if an association between current IED and current CUD (or cannabis use) is due to an attempt by an individual with IED to reduce aggression/irritability by using cannabis 19,25 or if the aggression observed in those with IED is associated with acute cannabis withdrawal<sup>21-24</sup> during intermittent periods of cannabis use. A third possibility is that heavy cannabis use has deleterious effects on brain function that lead to the development of IED. However, since the onset of IED was earlier than that of cannabis use disorder in IED+CUD subjects, cannabis may well be being used for its anti-aggressive properties <sup>19,25</sup> rather than the converse (i.e., IED emerging as a consequence of cannabis withdrawal or cannabis-related neurological damage). The same may be true for the relationship between tobacco use and tobacco use disorder and aggression. Laboratory

studies of human aggression report that smoking tobacco, in cigarette smokers, reduces aggressive responding to provocation<sup>26</sup>. In contrast, acute abstinence from smoking tobacco is associated with increased aggressive responding to provocation that is then blocked by administration of nicotine gum<sup>27</sup>.

The relationship between the three substances of abuse in this study is also noteworthy. Specifically, the risk of comorbid current IED and current TUD is lower in subjects with current AUD compared with those without current AUD. This may be due to the fact that alcohol use is widely known to increase aggressive behavior in humans <sup>10,11</sup> and, thus, aggressive events would be expected to be higher even in Non-IED subjects. That said, the risk of current IED is elevated above chance in subjects with current TUD and CUD regardless of current AUD.

#### STRENGTHS AND LIMITATIONS

The major strength is that these data were collected as part of a large, nationally representative, community sample using state of the art assessment tools which was blind to any of our hypotheses. Additionally, updating psychiatric diagnoses to meet DSM-5 criteria makes these data currently useful to researchers and clinicians alike. As with any investigation, a number of limitations must be noted. First, there are a modest number of subjects in some sub-analyses and this increases the risk of type 1 and 2 error depending on the finding. Second, these data are cross-sectional examination and this limits our interpretation for the causation of comorbidity. That said, the age of onset data strongly suggests that IED first occurs prior to the onset of SUD by several years. Third, these data were collected more than a decade ago and may not fully reflect more recent population wide changes, particularly in regard to SUD. However, there are no other epidemiologic data sets with more recently collected data with which to address these questions. Fourth, the NCS-R data set did not contain data regarding high-frequency/low-intensity aggressive outbursts (i.e., A<sub>1</sub> criteria for DSM-5 IED) and so information about subjects with IED of this type<sup>28,29</sup>, which might include an additional 10% of IED subjects<sup>9</sup>, was not available in this data set. However, about 75% of IED subjects with low-frequency/high-intensity aggressive outbursts (i.e., A<sub>2</sub> criteria for DSM-5 IED), as assessed in the NCS-R project, also have this form of aggressive outburst and IED subjects who only meet A<sub>1</sub> criteria do not differ from those who meet  $A_2$  criteria<sup>3</sup>.

#### CONCLUSION

The current presence of IED is associated with a statistically significant increase in the risk of current SUD. At the same time, the onset of IED precedes that of SUD is more than 90% of comorbid cases. This relationship between IED and SUD did not appear to be due to the presence, or absence, of current depressive or anxiety disorders. Accordingly, individuals with IED are at increased risk of developing substance use disorder at some time after the onset of IED. This may be because IED is an early indicator of a more severe impulsive externalizing liability that expresses in later substance use. If so, effective treatment of impulsive aggression, before the onset of substance misuse, may prevent, or delay, the development of SUD in young people.

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#### FINANCIAL DISCLOSURES

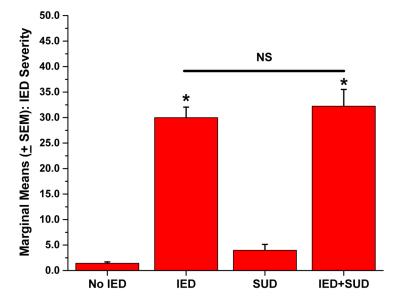
Dr. Coccaro reports being on the Scientific Advisory Board of Azevan Pharmaceuticals, Inc.; Dr. Lee reports being the recipient of a research grant from Azevan Pharmaceuticals, Inc.; Dr. Fanning has nothing to disclose.

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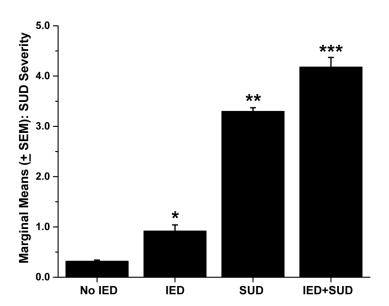


Figure 1. Top: Marginal means ( $\pm$  SEM) for IED severity after ANCOVA F[3,9273] = 90.87, p < .001. Asterisk indicates significant difference between IED and IED+SUD  $\underline{vs}$ . SUD and Non-IED (p < .001); the difference between IED and IED+SUD subjects was not significant (p = .562). Bottom: Marginal means ( $\pm$  SEM) for SUD severity after ANCOVA F[3,9273] = 734.10, p < .001. Asterisk indicates significant differences (p < .001) between all groups (IED+SUD > SUD > IED > Non-IED).

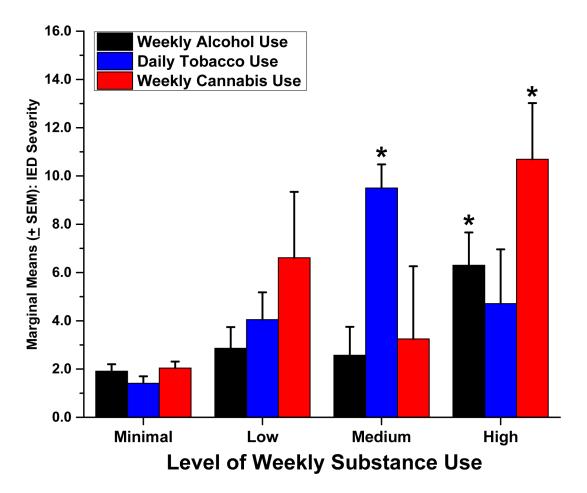


Figure 2. Marginal means ( $\pm$  SEM) for IED severity after ANCOVA by use groups comparing "minimal" with "low", "medium", and "high" use groups for alcohol, tobacco, and cannabis. Asterisks indicate significance levels (p < .05) for "high" vs. "minimal" use for alcohol and cannabis and "medium" vs. "minimal" use for tobacco.

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Table I

Characteristics of the Sample (N = 9,282)

Age (Mean)	44.7 ± 17.5 years		
Sex	44.6% Male 55.4% Female		
Race / Ethnicity	72.1% White 13.5% African-American 9.5% Hispanic 2.0% Asian 3.1% Other		
Education	14.8% < High School Degree 30.1% High School Degree 29.4% Some College 25.7% College Degree		
Marital Status	20.9% Single/Never Married 21.7% Separated/Divorced 57.3% Married/Cohabitating		
DSM-5 Intermittent Explosive Disorder	2.2% Current; 1.4% Past		
DSM-5 Substance Use Disorder	5.7% Current; 8.4% Past		
Current Substance Use	27.2% Alcohol 20.0% Tobacco 6.1% Cannabis		
Current SUD Subgroups	2.4% Alcohol (AUD) 3.4% Tobacco (TUD) 0.7% Cannabis (CUD)		

Table II

Comorbidity Rates of SUD and IED as a Function of Current Depressive Disorder and Current Anxiety Disorder.

	No Current Depressive Disorder	Current Depressive Disorder	No Current Anxiety Disorder	Current Anxiety Disorder
SUD in IED+	25.0% <sup>a</sup> (42/168)	43.6% <sup>a</sup> (17/39)	28.9% <sup>a</sup> (33/114)	28.0% <sup>a</sup> (23/93)
SUD in IED-	4.4% (365/8382)	15.6% (108/693)	3.4% (258/7578)	14.4% (215/1497)
Odds Ratio (95% CI)	4.90 <sup>b</sup> (3.33-7.19)	5.08 (2.48-10.42)	7.00 <sup>C</sup> (4.46-10.99)	2.21 (1.34-3.64)

Notes:

a:p < .001 (Fisher Exact Test);

b: p = .928 (z = 0.09) for difference in Odds Ratios between "No Current Depressive Disorder"; and "Current Depressive Disorder";

c:p < .01 (z = 3.06) for difference in Odds Ratios between "No Current Anxiety Disorder" and "Current Anxiety Disorder".

Table III

Comorbidity Rates of Current IED and Current Tobacco Use Disorder (TUD) and Cannabis Use Disorder (CUD) as a Function of Current Alcohol Use Disorder

	Current Tobacco Use Disorder		Current Cannabis Use Disorder	
	No Current	Current	No Current	Current
	Alcohol Use	Alcohol Use	Alcohol Use	Alcohol Use
	Disorder	Disorder	Disorder	Disorder
TUD or CUD	12.6% <sup>a</sup>	18.8%	2.9% <sup>a</sup>	31.3% <sup>b</sup> (10/32)
in IED+ Subjects	(22/175)	(6/32)	(5/175)	
TUD or CUD	2.8%	17.0%	0.3%	13.3%
in IED- Subjects	(251/8887)	(32/188)	(27/8887)	(25/188)
Odds Ratio (95% CI)	4.25 <sup>c</sup> (2.63-6.86)	1.07 (0.39-2.95)	4.42 <sup>d</sup> (1.63-11.99)	3.72 (1.42-9.77)

Notes

a: p < .001 (Fisher Exact Test);

*b:* p < .05 (Fisher Exact Test);

c: p < .01 (z = 2.83) for difference in Odds Ratios between "No Current Alcohol Use Disorder" and "Current Alcohol Use Disorder";

 $<sup>\</sup>frac{dz}{p} = .802 \ (z = 0.25) \ for \ difference \ in \ Odds \ Ratios \ between "No \ Current \ Alcohol \ Use \ Disorder".$