Survival Probabilities and Predictors of Major Depressive Episode Incidence Among Individuals With Various Types of Substance Use Disorders

Ahmed N. Hassan, MD, FRCPC, MPH,[a,b,c,*] and Bernard Le Foll, MD, PhD[a,b,c,d]

ABSTRACT

Objective: This study aimed to estimate the survival probabilities related to the occurrence of major depressive episodes (MDEs) after the onset of substance use disorders (SUDs) using data from the 2012–2013 National Epidemiologic Survey on Alcohol and Related Conditions-III.

Methods: The Alcohol Use Disorder and Associated Disabilities Interview Schedule-5 was used to diagnose SUD, and psychiatric diagnoses were based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition. Individuals with incidents of various SUDs with no prior history of MDEs (n = 5,987 with alcohol use disorder [AUD], 1,353 with cannabis use disorder [CUD], 351 with opioid use disorder [OUD], 827 with stimulant use disorder [STUD], and 5,363 with nicotine use disorder [NUD]) were included. The survival probabilities of these groups were compared to those of a control group without an SUD (n = 20,034). Outcome measures included the number of years from the age at SUD onset until MDE occurrence or the time of the interview.

Results: The probabilities of experiencing MDEs after 1 year were 3.56%, 4.80%, 7.78%, 8.46%, and 5.31% for AUD, CUD, OUD, STUD, and NUD, respectively. The groups differed statistically significantly from each other and from the control group ($P < .0001$). Individuals with AUD and STUD, respectively, had a lower and higher probability of having an MDE compared to those with other SUDs. Young age, family history of depression, anxiety disorder presence, and failure to achieve full remission consistently predicted an MDE for all substances.

Conclusions: The findings highlight that users of all studied substances have an increased probability of having an MDE over the lifespan.

J Clin Psychiatry 2021;82(5):20m13637

To cite: Hassan A, Le Foll B. Survival probabilities and predictors of major depressive episode incidence among individuals with various types of substance use disorders. *J Clin Psychiatry*. 2021;82(5):20m13637.

To share: https://doi.org/10.4088/JCP.20m13637

[a]Addictions Division, Centre for Addiction and Mental Health, Toronto, Ontario, Canada

[b]Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada

[c]Departments of Psychiatry, and Pharmacology and Toxicology, University of Toronto, Toronto, Ontario, Canada

[d]Department of Family and Community Medicine and Institute of Medical Sciences, University of Toronto, Toronto, Ontario, Canada

**Corresponding author:* Ahmed N. Hassan, MD, FRCPC, MPH, Department of Psychiatry, Centre for Addiction and Mental Health, 100 Stokes St, Third floor, M6J 1H4, Toronto, Ontario, Canada (ahmed.hassan@camh.ca).

The rate of occurrence of major depressive episodes (MDEs) has increased over the last decade. The co-occurring increase in substance use disorders (SUDs) has contributed to this increase in certain populations.[1] An estimated 10% of the burden of depression is attributed to an SUD.[2] National studies have indicated that 14.50% of individuals with an SUD experienced an MDE during a 12-month period,[3] with a much higher co-occurrence in clinical samples.[4] Comorbid depression affects the ability to achieve abstinence from substance use.[4] This comorbidity predicts poorer outcomes, including suicidality.[5,6]

The relationship between an SUD and an MDE can be described as bidirectional.[3] Longitudinal studies and meta-analyses[2,7–10] have indicated that the strongest relationship between an SUD and depression occurs when substance use appears first, rather than vice versa, and substance use increases the risk of depression. However, this potentially causal relationship remains understudied, and its probability of occurrence, associations, demographic differences, predictors, and longitudinal effect on depression warrant further investigations.[2]

The effect of an SUD on depression can be direct or indirect. An SUD commonly indicates that the substance might have affected an individual's social relationships, occupational performance, or academic functioning, and there may also be financial and legal ramifications.[11–13] These are well-known risk factors that could trigger an MDE. Physiologically, long-term substance use reduces dopamine receptor expression and dopamine release, leading to dopamine hypofunction,[14] which decreases euphoria or motivation to perform usual daily activities.[15] Prolonged substance use will also increase the cingulate cortex's sensitivity to stress, resulting in higher reactivity to stress and negative emotions, which increase the risk of depression.[15–17] Studies[18,19] have shown that individuals with alcohol use disorder (AUD), nicotine use disorder (NUD), or other SUDs have high levels of proinflammatory cytokines, which are positively associated with depression symptoms. Although all commonly abused substances appear to affect the immune system, their effects use different pathways that induce the production of different proinflammatory cytokines.[18] For example, a study[18] found that in individuals with AUD, the levels of interleukin-6 were associated with depression scores, while in individuals with disorders involving illicit substances, the levels of tumor necrosis factor-α were associated with depression scores.

Clinical Points

- Information on the lifespan probability of major depressive episode (MDE) occurrence after the onset of a substance use disorder (SUD) is highly valuable to the public.
- Patients with an SUD should be clearly informed of the risk of experiencing an MDE after screening for clinical risk factors.
- Clinicians should encourage their patients to achieve remission of an SUD to reduce the risk of developing an MDE.

A longitudinal study[20] on the first two waves (2001–2004) of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) identified a strong association between SUDs and MDEs. However, the survival probability was not assessed; the results did not differentiate between commonly abused substances such as cannabis and opioids and did not examine predictors associated with specific substances. Furthermore, the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), Fourth Edition, criteria were used to diagnose AUD and other SUDs, but the criteria have since been modified in the *DSM* Fifth Edition (*DSM-5*). A multinational study[21] with an older population (older than 55 years) found that the median survival time to the first MDE after alcohol abuse was 8.2 years. Another study,[22] based on national population cross-sectional data (2001–2003), reported that the SUD onset increased the odds of developing a mood disorder by 1- to 5-fold, with a mean onset of 11 years after SUD onset. Several studies have indicated a strong relationship between cannabis and the later development of depression, but only one study[23] had a lifelong prospective design, including 285 individuals, and found that early-onset use of cannabis is associated with depressive symptoms.

To our knowledge, there is no available information on the lifespan occurrence (survival probability) of MDEs after the onset of an SUD, and there is limited information on predictors of MDEs in association with various SUDs. This information is crucial for public health awareness and prevention of MDE; therefore, we performed the first study evaluating the survival probabilities of MDE occurrence after the onset of an SUD. We studied AUD and other common SUDs, including cannabis use disorder (CUD), stimulant use disorder (STUD), opioid use disorder (OUD), and NUD,[24] and assessed sociodemographic and clinical predictors of the first MDE for each of those 5 SUDs. We compared these survival probabilities to those of a control group who did not develop any of these SUDs.

METHODS

Population

The data were collected from the 2012–2013 NESARC-III.[25] A probability-based sampling technique randomly selected adults from the US population with certain race/ethnicities (Hispanic, Black, and Asian) being oversampled in this survey. Other details are described elsewhere.[25] This study received approval from the Centre for Addiction and Mental Health's Research Ethics Board (099-2019-01).

Exposure

The exposure group consisted of individuals with known first onset of prior to past-year AUD (n = 7,785), CUD (n = 1,748), OUD (opioid analgesics and heroin; n = 650), STUD (cocaine and amphetamines; n = 1,323), and NUD (n = 6,918). We excluded individuals who reported their first MDE prior to the onset of the SUD (n = 1,339 for AUD, 334 for CUD, 228 for OUD, 315 for STUD, and 1,021 for NUD) and those with missing data, ie, unknown age at onset for either the MDE or the SUD (n = 163 for AUD, 19 for CUD, 9 for OUD, 28 for STUD, and 534 for NUD). If the reported age at onset of the SUD was the same as that of the MDE, we excluded individuals who reported that the first MDE occurred prior to the onset of the SUD (n = 296 for AUD, 42 for CUD, 62 for OUD, and 153 for STUD) (this information was not available for NUD). The final sample consisted of 5,987 individuals with AUD, 1,353 with CUD, 351 with OUD, 827 with STUD, and 5,363 with NUD. Our control group included individuals without a lifetime diagnosis of any of the examined substances (n = 21,272). We excluded individuals who reported their first MDE prior to 19 years of age (the earliest age at onset of the SUDs examined) (n = 1,161) and those with missing data, ie, unknown age at onset of their MDE (n = 75). The final sample size consisted of 20,036 individuals in the control group.

Outcomes and Covariates

We defined an event as the occurrence of the first MDE (independent or substance-induced) from the time of diagnosis of AUD/CUD/OUD/STUD/NUD (origin time). The duration of the "observation period" was the number of years (in person-years) from the diagnosed onset of the SUD until the first MDE or the interview (right censoring); for the control group, the observation period was from 19 years of age until the first MDE or the interview.

The NESARC-III employed a fully structured interview, the Alcohol Use Disorder and Associated Disabilities Interview Schedule-5, to diagnose all SUDs; all other psychiatric diagnoses were based on the *DSM-5* criteria.

We used 19 questions from the NESARC-III to assess childhood adversities, which were adapted from two validated scales.[26,27] These questions are described in detail elsewhere.[28] The total score of childhood adversities was summed from the scores of all questions.

Statistical Analyses

The weighted frequencies and their 95% CIs are reported for each SUD group. The probability of an MDE was defined as the proportion of individuals who experienced an MDE at different time points in each SUD group. Survival analysis curves of all analyses are presented as one graph for each substance. We used discrete-time analysis to predict the

Table 1. Demographic and Clinical Variables of Individuals With Different Substance Use Disorders[a]

Characteristic	AUD (n = 5,987)	CUD (n = 1,353)	OUD (n = 351)	STUD (n = 827)	NUD (n = 5,363)
Age at the time of the interview, mean (95% CI), y	43.89 (43.32–44.47)	39.35 (38.48–40.21)	38.53 (36.74–40.32)	44.65 (43.55–45.76)	47.04 (46.48–47.60)
Substance use disorder age at onset, mean (95% CI), y	22.97 (22.77–23.17)	19.07 (18.75–19.40)	24.25 (23.23–25.28)	23.11 (22.52–23.71)	23.31 (22.98–23.64)
Female	36.25 (35.07–37.44)	32.87 (30.13–35.60)	37.99 (33.46–42.51)	38.34 (34.28–42.39)	41.72 (40.10–43.34)
White	77.54 (75.91–79.17)	73.77 (70.79–76.74)	80.20 (76.02–84.37)	78.20 (74.96–81.45)	79.37 (77.77–80.97)
Marital status					
Married for the duration of follow-up period	7.84 (7.08–8.60)	2.07 (1.20–2.94)	7.53 (5.26–9.80)	3.57 (2.32–4.82)	11.51 (10.30–12.71)
Other (separated/divorced or married during follow-up)	69.55 (67.92–71.18)	66.49 (63.59–69.39)	60.51 (55.08–65.94)	74.70 (71.17–78.22)	69.37 (67.58–71.17)
Never married	22.61 (21.10–24.12)	31.44 (28.54–34.34)	31.96 (26.57–37.34)	21.74 (18.40–25.08)	19.12 (17.71–20.53)
Unemployed, mean (95% CI), wk	34.67 (29.45–39.90)	33.44 (24.13–42.75)	66.46 (40.37–92.56)	49.85 (37.64–62.07)	50.32 (44.38–56.26)
High school education or less	28.62 (26.94–30.30)	31.78 (28.74–34.82)	38.62 (33.01–44.24)	33.86 (30.07–37.65)	36.82 (34.76–38.89)
No. of use disorder criteria when diagnosed, mean (95% CI)	5.63 (5.55–5.71)	5.50 (5.36–5.63)	6.46 (6.05–6.87)	6.71 (6.38–7.04)	5.01 (4.93–5.10)
Achieved remission prior to MDE	8.70 (7.78–9.62)	14.20 (12.42–15.99)	55.69 (50.32–61.05)	11.58 (8.83–14.33)	33.92 (32.21–35.64)
Family history of AUD/SUD	53.52 (51.98–55.10)	49.25 (46.28–52.23)	56.32 (50.84–61.80)	48.66 (44.03–53.29)	62.16 (60.53–63.80)
Family history of MDD	50.52 (49.08–51.96)	61.84 (58.82–64.86)	59.14 (53.02–65.27)	53.42 (49.48–57.36)	50.17 (48.46–51.88)
Borderline personality disorder	17.05 (15.97–18.12)	27.48 (24.45–30.51)	36.15 (29.86–42.43)	31.26 (27.86–34.66)	18.16 (16.80–19.52)
Schizotypal personality disorder	6.06 (5.46–6.66)	12.28 (10.43–14.13)	16.00 (11.99–20.02)	11.45 (9.28–13.63)	7.13 (6.36–7.91)
Antisocial personality disorder	5.31 (4.62–5.99)	11.60 (9.16–14.04)	20.48 (15.44–25.52)	13.11 (9.93–16.29)	5.99 (5.11–6.86)
Presence of anxiety disorder(s)					
1 disorder	15.62 (14.46–16.78)	18.87 (15.75–21.99)	23.37 (18.09–28.65)	20.91 (17.15–24.66)	17.75 (16.44–9.07)
2 disorders	5.14 (4.42–5.85)	6.79 (4.94–8.64)	7.02 (4.08–9.96)	7.38 (5.28–9.48)	5.30 (4.51–6.09)
3 disorders	1.42 (1.01–1.82)	2.38 (1.38–3.39)	2.60 (0.33–4.86)	2.61 (1.38–3.85)	1.94 (1.49–2.39)
4 disorders	0.76 (51–1.01)	1.46 (0.42–2.51)	1.65 (0.05–3.24)	1.12 (0.37–1.87)	0.85 (0.19–0.55)
5 disorders	0.23 (0.12–0.35)	0.04 (0.00–0.13)	0.49 (0.00–1.18)	0.25 (0.09–0.41)	0.37 (0.19–0.55)
Lifetime disorders					
Bipolar disorder	3.56 (2.89–4.23)	5.71 (4.30–7.12)	7.63 (4.31–10.96)	7.32 (5.12–9.52)	3.99 (3.33–4.65)
PTSD	8.44 (7.58–9.29)	13.37 (11.26–15.48)	20.32 (15.10–25.54)	16.41 (12.79–20.03)	10.28 (9.33–11.23)
AUD	…	78.72 (76.25–81.19)	79.90 (75.31–84.48)	80.43 (77.15–83.71)	57.99 (56.03–59.96)
CUD	16.81 (15.60–18.02)	…	40.97 (35.38–46.56)	39.95 (35.23–44.67)	17.51 (16.08–18.94)
OUD	5.36 (4.63–6.09)	12.60 (10.46–14.75)	…	17.25 (14.47–20.04)	5.53 (4.82–6.24)
STUD	10.91 (9.99–11.84)	25.83 (23.03–28.62)	41.11 (35.61–46.61)	…	5.62 (4.77–6.46)
NUD	52.71 (50.81–54.62)	70.90 (67.13–74.67)	74.85 (70.77–78.94)	79.50 (76.14–82.87)	…
Childhood adversities score, mean (95% CI)	27.65 (27.31–28.00)	29.49 (28.87–30.10)	30.94 (29.85–32.03)	30.51 (29.63–31.39)	28.21 (27.88–28.53)

[a]Values are shown as % (95% CI) unless otherwise noted.
Abbreviations: AUD = alcohol use disorder, CUD = cannabis use disorder, MDE = major depressive episode, NUD = nicotine use disorder, OUD = opioid use disorder, PTSD = posttraumatic stress disorder, STUD = stimulant use disorder, SUD = substance use disorder.

occurrence of MDEs because this method is reportedly the best when there are many individuals experiencing an event at a particular time and when the timing of the event is not specific, as was the case in our sample.[29] We used a semiparametric Cox regression hazards model that does not make any assumption regarding the probability distribution of event times.[29]

Certain predictor variables that might affect the occurrence of MDEs were selected for inclusion in the model, as previously reported. These predictors were age at SUD onset, age at the time of the interview, sex, employment status,[4] marital status, ethnicity, family history of depression and SUD,[5] level of education, and childhood adversities.[30] We also included the number of satisfied SUD criteria at the time of occurrence of the disorder. Time-dependent variables were lifetime history of at least one anxiety disorder (generalized anxiety disorder, social anxiety disorder, panic disorder, agoraphobia or specific phobia),[31] posttraumatic stress disorder, bipolar disorder, and other lifetime SUDs. The exposure groups could have lifetime diagnoses of a single SUD or multiple SUDs. The effect of each added SUD was also used as a predictor variable for the occurrence of MDE. All of these variables were tested for violation of the proportional hazards model using Schoenfeld residuals. If any variable was significant, then we estimated the extended model by testing the interaction of this variable with time and whether the coefficient was significant, which allowed for non-proportional hazards.

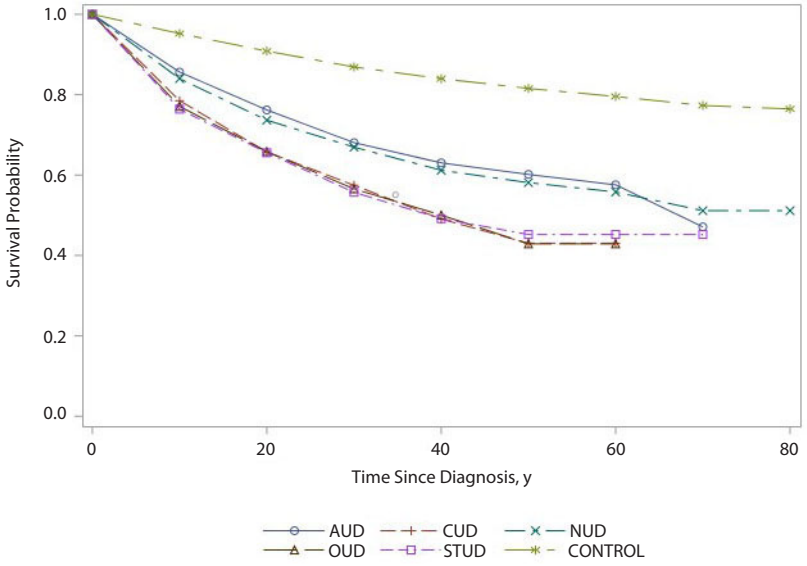
Taylor series linearization methods implemented in Statistical Analysis Software (SAS) version 9.4 (2015) were used in the analysis to account for the complex survey design. The level of significance was set at $P < .05$.

RESULTS

Demographics of the Sample

Table 1 demonstrates the demographic and clinical information for each of the 5 groups. The earliest age at SUD onset was for cannabis (19.07 years), followed by alcohol (22.97 years), stimulants (23.11 years), nicotine (23.31 years), and opioids (24.25 years). The majority ethnic group was White for all 5 SUD groups. The percentage of

Figure 1. Survival Probability of Developing a First Major Depressive Episode After the Onset of Substance Use Disorder[a]



[a]Wilcoxon $P < .0001$.
Abbreviations: AUD = alcohol use disorder, CUD = cannabis use disorder, OUD = opioid use disorder, NUD = nicotine use disorder, STUD = stimulant use disorder.

Table 2. Probability of Major Depressive Episode Incidence at Each Time Point for Each Substance Use Disorder[a]

Time Point	Alcohol Use Disorder (n = 5,987)	Cannabis Use Disorder (n = 1,353)	Opioid Use Disorder (n = 351)	Stimulant Use Disorder (n = 827)	Nicotine Use Disorder (n = 3,563)	Control Group (n = 20,036)
Within the same year	1.62 (1.32–1.96)	2.14 (1.47–3.02)	4.84 (2.93–7.45)	4.96 (3.62–6.59)	3.26 (2.81–3.76)	0.45 (0.36–0.55)
Year 1	3.56 (3.11–4.05)	4.80 (3.75–6.04)	7.78 (5.27–10.91)	8.46 (6.69–10.49)	5.31 (4.74–5.94)	0.93 (0.81–1.08)
Year 2	5.30 (4.75–5.89)	7.65 (6.31–9.15)	10.81 (7.80–14.38)	11.26 (9.22–13.53)	7.09 (6.42–7.80)	1.34 (1.19–1.51)
Year 3	6.94 (6.31–7.61)	10.36 (8.79–12.07)	12.09 (8.88–15.83)	13.47 (11.24–15.90)	8.33 (7.61–9.10)	1.89 (1.71–2.09)
Year 4	8.35 (7.65–9.08)	12.20 (10.50–14.03)	13.46 (10.04–17.38)	15.33 (12.96–17.88)	9.68 (8.90–10.50)	2.30 (2.10–2.52)
Year 5	9.68 (8.93–10.47)	14.01 (12.19–15.96)	15.98 (12.21–20.22)	16.84 (14.37–19.49)	11.03 (10.20–11.90)	2.66 (2.44–2.89)
Year 6	10.80 (10.00–11.63)	15.78 (13.85–17.84)	16.76 (12.87–21.09)	17.75 (15.21–20.45)	12.27 (11.39–13.19)	3.31 (3.07–3.57)
Year 7	11.92 (11.08–12.79)	17.73 (15.67–19.89)	18.82 (14.64–23.41)	19.33 (16.69–22.12)	13.48 (12.55–14.44)	3.76 (3.50–4.04)
Year 8	12.75 (11.88–13.66)	19.09 (16.96–21.32)	21.10 (16.59–25.98)	21.36 (18.59–24.26)	14.43 (13.47–15.42)	4.20 (3.92–4.49)
Year 9	13.88 (12.97–14.83)	20.98 (18.74–23.31)	22.04 (17.41–27.03)	22.77 (19.91–25.75)	15.52 (14.53–16.55)	4.75 (4.45–5.06)
Year 10	15.20 (14.23–16.19)	21.95 (19.66–24.33)	24.98 (19.96–30.30)	24.65 (21.69–27.73)	16.88 (15.84–17.95)	5.13 (4.82–5.45)

[a]All values are shown as % (95% CI).

female individuals ranged from 32.87% to 41.72% across the 5 groups. The average severity of the SUD was moderate in the AUD, NUD, and CUD groups and severe (≥ 6 criteria) in the OUD and STUD groups.

Probability of MDE Development After the Onset of SUD

The probability of MDE development within the same year was 1.62%, 2.14%, 4.84%, 4.96%, 3.26%, and 0.45% for the AUD, CUD, OUD, STUD, NUD, and control groups, respectively. The probability for an MDE after 1 year was 3.56%, 4.80%, 7.78%, 8.46%, 5.31%, and 0.93% for the AUD, CUD, OUD, STUD, NUD, and control groups, respectively. The 5-year probability of MDE development was 9.68%, 14.01%, 15.98%, 16.84%, 11.03%, and 2.66% after the onset of AUD, CUD, OUD, STUD, and NUD and in the control group, respectively. Figure 1 presents the survival probabilities for the 5 groups and the control group. Table 2 presents the probabilities and CIs for the first 10 years for each SUD group and the control group. Log rank tests of equality between the groups revealed statistically significant differences ($\chi^2 = 2160.50$, $P < .0001$).

Predictors of MDEs

Supplementary Table 1 and Table 3 demonstrate the univariate and multivariate discrete-survival analyses, respectively, for the 5 substance groups.

Sociodemographic Predictors

Young age at the time of the interview predicted MDEs associated with the use of all 5 substances. Each year younger at the time of the interview increased the risk of developing an MDE by 4% for all 5 groups. Female sex was a predictor of MDEs in both the univariate and multivariate analyses for

Table 3. Multivariate Analysis of Sociodemographic and Clinical Predictors of a Major Depressive Episode in Individuals With Different Substance Use Disorders[a]

Characteristics	Alcohol use Disorder (n = 5,987) HR (95% CI)	Cannabis use Disorder (n = 1,353) HR (95% CI)	Opioid use Disorder (n = 351) HR (95% CI)	Stimulant use Disorder (n = 827) HR (95% CI)	Nicotine use Disorder (n = 3,563) HR (95% CI)
Age at time of the interview	**0.97 (0.96–0.98)**	**0.95 (0.94–0.96)**	**0.94 (0.91–0.96)**	**0.96 (0.94–0.97)**	**0.96 (0.95–0.97)**
SUD age at onset	**1.03 (1.01–1.04)**	1.02 (0.99–1.05)	**1.05 (1.02–1.08)**	1.01 (0.98–1.05)	**1.03 (1.03–1.04)**
No. of use disorder criteria when diagnosed	**1.07 (1.03–1.11)**	**1.09 (1.05–1.14)**	**1.11 (1.03–1.19)**	1.05 (1.00–1.11)	**1.08 (1.05–1.11)**
Achieving full remission prior to MDE	**0.36 (0.31–0.42)**	**0.26 (0.21–0.34)**	**0.20 (0.12–0.34)**	**0.48 (0.35–0.65)**	**0.32 (0.28–0.38)**
Female	**1.37 (1.20–1.57)**	**1.35 (1.03–1.78)**	0.97 (0.59–1.57)	1.39 (1.00–1.94)	**1.65 (1.41–1.91)**
White	1.12 (0.98–1.28)	**1.57 (1.17–2.10)**	1.08 (0.74–1.57)	0.88 (0.62–1.26)	1.02 (0.89–1.17)
Marital status					
Married for the duration of follow-up period	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Other (separated/divorced or married during follow-up)	1.21 (0.87–1.68)	2.36 (0.77–7.25)	2.31 (0.82–6.49)	**4.82 (1.28–18.17)**	**1.52 (1.15–2.00)**
Never married	1.01 (0.69–1.48)	1.96 (0.61–6.34)	1.88 (0.62–5.71)	**4.34 (1.09–17.25)**	**1.43 (1.02–2.01)**
Number of weeks unemployed	1.00 (1.00–1.00)	1.00 (0.99–1.00)	1.00 (0.99–1.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)
Education[b]	1.01 (0.98–1.04)	1.06 (0.99–1.13)	1.08 (0.96–1.21)	0.95 (0.86–1.05)	1.01 (0.98–1.04)
Family history of AUD/SUD	1.11 (0.97–1.28)	0.99 (0.78–1.26)	1.46 (0.82–2.63)	1.18 (0.94–1.62)	1.04 (0.90–1.20)
Family history of MDD	**2.11 (1.80–2.47)**	**1.84 (1.44–2.35)**	**2.46 (1.47–4.10)**	**2.00 (1.55–2.60)**	**1.96 (1.67–2.30)**
Borderline personality disorder	**1.54 (1.29–1.83)**	1.26 (0.93–1.73)	1.28 (0.83–1.98)	1.00 (0.69–1.45)	**1.50 (1.24–1.80)**
Schizotypal personality disorder	0.98 (0.76–1.26)	0.75 (0.50–1.14)	0.73 (0.33–1.60)	0.94 (0.58–1.55)	1.08 (0.88–1.32)
Antisocial personality disorder	0.98 (0.77–1.25)	0.97 (0.67–1.40)	0.78 (0.36–1.69)	1.22 (0.84–1.76)	0.90 (0.72–1.12)
Presence of anxiety disorder(s)					
1 disorder	**1.93 (1.70–2.21)**	**1.66 (1.31–2.10)**	1.11 (0.59–2.12)	**1.77 (1.26–2.49)**	**1.71 (1.48–1.98)**
2 disorders	**1.65 (1.26–2.16)**	1.35 (0.84–2.17)	**2.51 (1.11–5.68)**	**1.92 (1.15–3.21)**	**1.75 (1.39–2.22)**
3 disorders	**2.04 (1.38–3.01)**	**1.88 (1.12–3.18)**	1.37 (0.45–4.22)	1.38 (0.59–3.26)	**2.08 (1.51–2.86)**
4 disorders	**2.47 (1.61–3.90)**	**4.15 (1.57–11.00)**	3.87 (0.55–27.29)	**2.62 (1.27–5.39)**	1.36 (0.97–1.91)
5 disorders	**2.87 (1.21–6.77)**	**4.21 (2.63–6.75)**	2.36 (0.09–60.32)	**2.45 (1.33–4.51)**	**2.27 (1.36–3.79**
Lifetime disorders					
Bipolar disorder	1.01 (0.75–1.34)	1.22 (0.82–1.81)	0.47 (0.19–1.15)	1.50 (0.91–2.48)	1.17 (0.91–1.50)
PTSD	1.22 (0.98–1.52)	1.05 (0.75–1.46)	1.15 (0.67–1.97)	1.32 (0.87–2.00)	1.06 (0.88–1.29)
Alcohol use disorder		0.84 (0.62–1.13)	0.90 (0.47–1.72)	0.90 (0.61–1.33)	1.07 (0.93–1.22)
Cannabis use disorder	1.11 (0.95–1.30)		**2.07 (1.23–3.50)**	1.15 (0.85–1.54)	1.9 (0.93–1.27)
Opioid use disorder	0.97 (0.78–1.21)	1.10 (0.76–1.62)		0.85 (0.57–1.28)	0.99 (0.79–1.25)
Stimulant use disorder	**0.73 (0.55–0.96)***	1.07 (0.77–1.48)	1.07 (0.67–1.70)		1.11 (0.89–1.39)
Nicotine use disorder	1.05 (0.94–1.19)	1.30 (0.97–1.73)	1.01 (0.57–1.77)	1.33 (0.90–1.95)	
Childhood adversities	1.00 (0.99–1.01)	1.01 (0.99–1.02)	1.00 (0.98–1.02)	1.00 (0.99–1.02)	**1.01 (1.00–1.01)**

[a]All values are shown as HR (95% CI). Bold indicates statistical significance ($P < .05$).
[b]Education was evaluated as a continuous variable.
*Interaction with time.
Abbreviations: AUD = alcohol use disorder, HR = hazard ratio, MDD = major depressive disorder, MDE = major depressive episode, PTSD = posttraumatic stress disorder, SUD = substance use disorder.

AUD, NUD, and CUD. Individuals who were never married had higher hazard ratios for MDEs in all groups, except for CUD, in the univariate analysis. However, marital status was not a statistically significant predictor after adjusting for sociodemographic and clinical variables, except for STUD and NUD. Being White was associated with a higher risk for developing an MDE only in the CUD group.

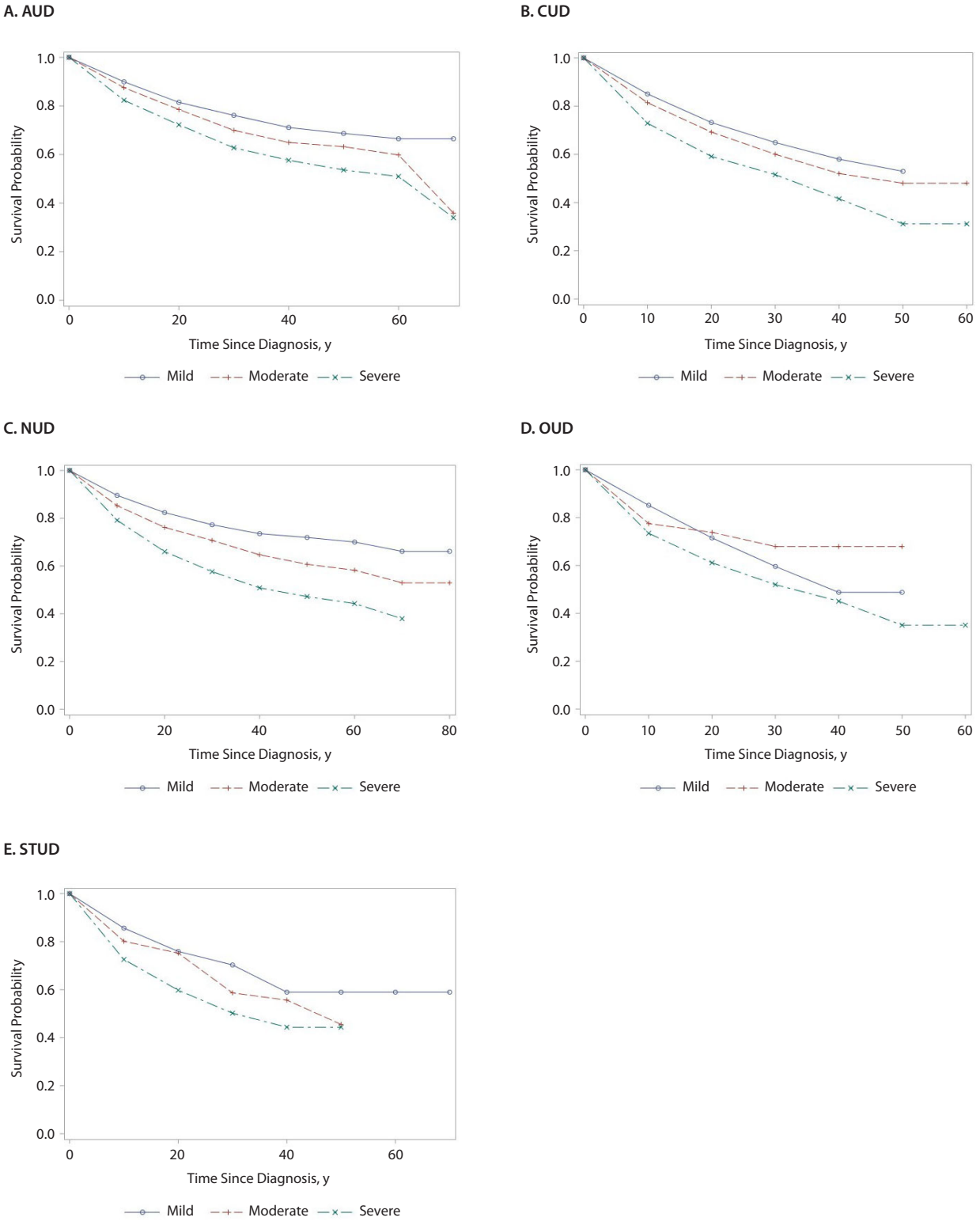
Clinical Predictors

Age at SUD onset was a predictive factor for MDE in the AUD ($P = .01$), NUD ($P < .01$), and OUD ($P < .01$) groups after controlling for other covariates. Disorder severity (based on the number of SUD criteria met) predicted MDEs for all groups except for the STUD group (AUD: $P = .03$, CUD: $P < .01$, OUD: $P = .01$, STUD: $P = .08$, NUD: $P < .01$). For each additional criterion met for AUD, NUD, CUD, and OUD, there was an increased risk for MDE onset of 7%, 8%, 9%, and 11%, respectively. We conducted an additional analysis comparing the probability of first MDEs among each SUD based on different severities (Figure 2). Individuals with severe SUD had the highest probability of depression compared to those with moderate and mild SUDs for each substance. The test of equality among the different severities showed statistically significant differences for all substances except for opioids (Figure 2).

Achievement of full SUD remission prior to the onset of the first MDE was a protective factor, which remained statistically significant after controlling for all covariates in all 5 groups (all groups, $P < .01$).

Family history of a first-degree relative with major depressive disorder predicted an MDE after the onset of substance use for all substances (all $P < .01$). The hazard ratio for developing an MDE in an individual with AUD and a family history of depression was 2.11, and 1.84, 1.96, 2.46, and 2.00 for those with CUD, NUD, OUD, and STUD, respectively. A diagnosis of borderline personality disorder predicted an MDE for AUD and NUD ($P < .01$). The presence of 2 or more anxiety disorders consistently predicted an MDE for most substances, with a hazard ratio of 1.65 or higher. The comorbidity of CUD and OUD increased the probability of MDE occurrence after controlling for all covariates ($P = .01$). Childhood adversity was a predictor of

Figure 2. Survival Probability of a First Major Depressive Episode per Each Substance Use Disorder Based on Its Severity[a]



[a]Each figure shows the probabilities for individuals with that disorder of varying severity: AUD: Wilcoxon $P < .001$, CUD: Wilcoxon $P < .001$, NUD: Wilcoxon $P < .001$, OUD: Wilcoxon $P = .117$, STUD: Wilcoxon $P < .001$.

Abbreviations: AUD = alcohol use disorder, CUD = cannabis use disorder, OUD = opioid use disorder, NUD = nicotine use disorder, STUD = stimulant use disorder.

MDEs in AUD, NUD, CUD, and STUD in the univariate analysis, but it lost its significance after controlling for other covariates in all groups except for NUD.

DISCUSSION

Multiple studies have reported that the SUD onset increases the odds of experiencing an MDE.[21,22,32] Here, based on a national representative sample, we estimated that the probability of a first MDE after the onset of AUD, CUD, OUD, STUD, and NUD was 3.6%, 4.8%, 7.8%, 8.5%, and 5.3%, after 1 year from the diagnosed onset. These probabilities were significantly different from the probability of MDE in the control group without SUD (0.9%). The incident rate of MDE in the first year for AUD was similar to rates reported after heavy drinking in a Canadian national sample.[33] After 10 years from the diagnosed onset, the respective probabilities were 15.2%, 22.0%, 25.0%, 24.7%, and 16.9%, indicating that in individuals with AUD, the risk of MDE steadily increases with time but remains lower than the risk in individuals with NUD, OUD, STUD, and CUD. The highest probability of an MDE was seen in the STUD group. The initial risk associated with CUD was similar to that associated with AUD, but then increased substantially over time, approaching the rates seen in individuals with OUD and STUD. This information is highly important for individuals with CUD who commonly use cannabis for years, as it raises awareness of the risk of not managing the disorder earlier. The legal status of the substance; the effect of the SUD on the social, occupational, or academic domains; and the aforementioned different pathways of its physiologic effect can possibly explain the different risks for MDE across substances. These risks significantly increased in our sample if other variables predictive of an MDE were also present.

Among the sociodemographic variables, female sex was a predictor for an MDE in AUD, NUD, and CUD, consistent with the findings of other studies showing that female sex predicted MDEs.[21] Younger age was a strong predictor of MDEs for all substances, which might reflect the major impact of SUD diagnoses on the lives of young individuals and the developing brain relative to that in older populations, but it might also reflect lower recall bias.

The strong predictability of a family history of depression suggests that AUD and other SUDs trigger a genetic allele that is associated with depression.[34] Previous studies[35,36] have found that certain polymorphisms predispose individuals to both AUD and MDEs. There is also evidence for shared genetic factors associated with CUD, AUD, and MDE,[37] and the interaction between environmental and genetic factors plays a role in the development of SUDs and MDEs. For example, individuals with low expression of the serotonin transporter genotype expressed high stress reactivity when exposed to stress as well as preference to use substances and exhibited more depressive symptoms.[38] Another study[39] showed that the association between alcohol use and subsequent depression is high in female carriers of the serotonin transporter 5-HTTLPR short allele. This increased risk can be useful for individuals presenting at the clinic who have an SUD and family history of depression.

High levels of anxiety symptoms were also associated with MDEs in previous studies.[20,31,40] Here, we found that the presence of at least 1 anxiety disorder predicted MDEs in all groups. This finding highlights the importance of screening for multiple comorbid anxiety disorders and trauma/posttraumatic stress disorder in patients presenting for SUD treatment.

Individuals who did not achieve full remission were at 2, 3, 4, and 5 times higher risk for developing MDEs than individuals who achieved full remission for STUD, AUD/NUD, CUD, and OUD, respectively, reflecting the importance of helping patients achieve full SUD remission to prevent an MDE. This information can be very motivating for individuals with an SUD to achieve remission to prevent an MDE.

Previous studies have reported that the more severe the SUD, the greater the risk of developing depression.[41] Here, we estimated that for each level of additional severity based on the *DSM-5* criteria for diagnosing SUD, the hazard risk of developing depression increased by 7% for AUD, 8% for NUD, 9% for CUD, and 11% for OUD. STUD was unaffected by the number of satisfied criteria, possibly because there was a higher average number of criteria met when STUD was diagnosed (severe) compared to when AUD and CUD (moderate) were diagnosed. The lack of relationship between level of severity and risk of developing depression could also be attributable to the smaller size of the STUD group relative to the sizes of the AUD and CUD groups. Figure 2 shows the significant probability of developing an MDE in individuals with severe AUD in comparison with mild AUD in the presence of other risk factors in both groups. We could propose that there is value in aiming to decrease the severity criteria to prevent an MDE, but this cannot be confirmed from our data. Therefore, we recommend early intervention including screening for SUD and engaging patients in treatment if an SUD is found, which could involve medication to reduce cravings, withdrawal, or overdose, and it can be combined with psychosocial treatment, such as motivational interviewing, the 12-step program, cognitive-behavioral therapy, and referral to a social worker.

Limitations

This analysis used retrospective data, which might raise the risk of recall bias. We excluded individuals who did not remember their age at the onset of the MDE or SUD. The standard survival analysis methods assume that right censoring is non-informative, meaning that a person who had not developed depression by the time of the interview is not at risk; this assumption might have introduced bias given the varied reporting times in our individuals.[29] However, our participants reported at least 1 year's worth of information prior to the interview, so the probabilities over the first year may be more accurate. We also included and controlled for age at the time of the interview to reduce these confounders. Another limitation in our model was missing information

regarding important sociodemographic variables, including income and precise marital status at the time of diagnosis, and important clinical variables such as the amount and duration of substances used, which are reported predictors of depression.[42]

In summary, we reported, for the first time, the survival probabilities of MDE occurrence after an SUD diagnosis. AUD, NUD, and CUD are associated with a lower probability of MDEs compared to OUD and STUD, but the risk steadily increases over time for all substances. The probability of MDEs in CUD rises rapidly after 1 year of use, a rate similar to that of OUD and STUD. Young age, family history of depression, presence of at least 1 anxiety disorder, and failure to achieve full remission consistently predicted MDEs for all substances. Public awareness and psychoeducation on the probability of experiencing an MDE after SUD onset can be very useful information for the prevention of the development of SUDs for those who use substances. They could also motivate those with already developed SUDs to seek treatment and achieve remission. Identifying SUDs and screening for risk factors are essential for preventing MDEs, especially for those with multiple risk factors. Longitudinal studies are needed to assess other clinical variables, including patterns of drug use and quantity consumed, which could predict or prevent an MDE for individuals receiving various treatments.

Submitted: August 7, 2020; accepted February 22, 2021.

Published online: July 27, 2021.

Potential conflicts of interest: **Dr Le Foll** is supported by a clinician-scientist award from the Department of Family and Community Medicine at University of Toronto and Addiction Psychiatry Chair from University of Toronto. He has obtained funding from Pfizer (GRAND Awards, including salary support) for investigator-initiated projects. He has received some in-kind donation of cannabis product from Aurora and medication donation from Pfizer and Bioprojet and was provided a coil for transcranial magnetic stimulation study from Brainsway. He has obtained industry funding from Canopy (through research grants handled by the Centre for Addiction and Mental Health or University of Toronto), Bioprojet, ACS, and Alkermes. He has received in-kind donations of nabiximols from GW Pharma for past studies funded by the Canadian Institutes of Health Research and the National Institutes of Health. **Dr Hassan** has no potential conflicts of interest relevant to the subject of this article.

Funding/support: None.

Supplementary material: Available at PSYCHIATRIST.COM.

REFERENCES

1. Conway KP, Compton W, Stinson FS, et al. Lifetime comorbidity of *DSM-IV* mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2006;67(2):247–257.
2. Boden JM, Fergusson DM. Alcohol and depression. *Addiction*. 2011;106(5):906–914.
3. Grant BF, Stinson FS, Dawson DA, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders. *Arch Gen Psychiatry*. 2004;61(8):807–816.
4. Lejoyeux M, Lehert P. Alcohol-use disorders and depression: results from individual patient data meta-analysis of the acamprosate-controlled studies. *Alcohol Alcohol*. 2011;46(1):61–67.
5. Quello SB, Brady KT, Sonne SC. Mood disorders and substance use disorder: a complex comorbidity. *Sci Pract Perspect*. 2005;3(1):13–21.
6. Davis L, Uezato A, Newell JM, et al. Major depression and comorbid substance use disorders. *Curr Opin Psychiatry*. 2008;21(1):14–18.
7. Fergusson DM, Boden JM, Horwood LJ. Tests of causal links between alcohol abuse or dependence and major depression. *Arch Gen Psychiatry*. 2009;66(3):260–266.
8. Flensborg-Madsen T, Mortensen EL, Knop J, et al. Comorbidity and temporal ordering of alcohol use disorders and other psychiatric disorders: results from a Danish register-based study. *Compr Psychiatry*. 2009;50(4):307–314.
9. Gage SH, Hickman M, Heron J, et al. Associations of cannabis and cigarette use with depression and anxiety at age 18: findings from the Avon Longitudinal Study of Parents and Children. *PLoS One*. 2015;10(4):e0122896.
10. Anderson HO, Libby AM. Depression with and without comorbid substance dependence in a child welfare sample of young adults. *Depress Res Treat*. 2011;2011:475248.
11. Lander L, Howsare J, Byrne M. The impact of substance use disorders on families and children: from theory to practice. *Soc Work Public Health*. 2013;28(3–4):194–205.
12. Andrews SB, Normand J, Lempert RO, et al. *Under the Influence?* Vol. 48. Drugs and the American Work Force; 1995.
13. Balsa AI, Giuliano LM, French MT. The effects of alcohol use on academic achievement in high school. *Econ Educ Rev*. 2011;30(1):1–15.
14. Volkow ND, Fowler JS, Wang G-J, et al. Dopamine in drug abuse and addiction: results of imaging studies and treatment implications. *Arch Neurol*. 2007;64(11):1575–1579.
15. Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. *N Engl J Med*. 2016;374(4):363–371.
16. Zakiniaeiz Y, Scheinost D, Seo D, et al. Cingulate cortex functional connectivity predicts future relapse in alcohol dependent individuals. *Neuroimage Clin*. 2016;13:181–187.
17. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Psiquiatr Biol*. 2010;17(2):71–80.
18. Martinez P, Lien L, Zemore S, et al. Circulating cytokine levels are associated with symptoms of depression and anxiety among people with alcohol and drug use disorders. *J Neuroimmunol*. 2010;17(2):71–80.
19. Vargas HO, Nunes SOV, de Castro MRP, et al. Oxidative stress and inflammatory markers are associated with depression and nicotine dependence. *Neurosci Lett*. 2013;544:136–140.
20. Grant BF, Goldstein RB, Chou SP, et al. Sociodemographic and psychopathologic predictors of first incidence of *DSM-IV* substance use, mood and anxiety disorders: results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions. *Mol Psychiatry*. 2009;14(11):1051–1066.
21. Keyes KM, Allel K, Staudinger UM, et al. *Alcohol Consumption Predicts Incidence of Depressive Episodes across 10 Years among Older Adults in 19 Countries*. Vol. 148. 1st ed. Elsevier Inc.; 2019.
22. Kenneson A, Funderburk JS, Maisto SA. Substance use disorders increase the odds of subsequent mood disorders. *Drug Alcohol Depend*. 2013;133(2):338–343.
23. Schoeler T, Theobald D, Pingault JB, et al. Developmental sensitivity to cannabis use patterns and risk for major depressive disorder in mid-life: findings from 40 years of follow-up. *Psychol Med*. 2018;48(13):2169–2176.
24. Grant BF, Saha TD, Ruan WJ, et al. Epidemiology of *DSM-5* drug use disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions-III. *JAMA Psychiatry*. 2016;73(1):39–47.
25. Grant BF, Goldstein RB, Smith SM, et al. The Alcohol Use Disorder and Associated Disabilities Interview Schedule-5 (AUDADIS-5): reliability of substance use and psychiatric disorder modules in a general population sample. *Drug Alcohol Depend*. 2015;148:27–33.
26. Bernstein DP, Fink L, Handelsman L, et al. Initial reliability and validity of a new retrospective measure of child abuse and neglect. *Am J Psychiatry*. 1994;151(8):1132–1136.
27. Straus MA. Measuring intrafamily conflict and violence: the Conflict Tactics (CT) scales. *J Marriage Fam*. 1979;41(1):75–88.
28. Keyes KM, Eaton NR, Krueger RF, et al. Childhood maltreatment and the structure of common psychiatric disorders. *Br J Psychiatry*. 2012;200(2):107–115.
29. Allison PD. Event history and survival analysis. In: Hancock GR, Stapleton LM, Mueller RO, eds *The Reviewer's Guide to Quantitative Methods in the Social Sciences*. New York, NY: Routledge; 2019.
30. Peters AT, Shankman SA, Deckersbach T, et al. Predictors of first-episode unipolar major depression in individuals with and without sub-threshold depressive symptoms: a prospective, population-based study. *Psychiatry Res*. 2015;230(2):150–156.
31. Bittner A, Goodwin RD, Wittchen HU, et al. What characteristics of primary anxiety disorders predict subsequent major depressive disorder? *J Clin Psychiatry*. 2004;65(5):618–626, quiz 730.
32. Brooks JM, Petersen C, Kelly SM, et al. Likelihood of depressive symptoms in US older adults by prescribed opioid potency: National Health and Nutrition Examination Survey 2005–2013. *Int J Geriatr Psychiatry*. 2019;34(10):1481–1489.
33. Wang J, Patten SB. Prospective study of frequent heavy alcohol use and the risk of

major depression in the Canadian general population. *Depress Anxiety*. 2002;15(1):42–45.
34. Langbehn DR, Philibert R, Caspers KM, et al. Association of a D2S2944 allele with depression specifically among those with substance abuse or antisocial personality. *Drug Alcohol Depend*. 2006;83(1):33–41.
35. Luo X, Kranzler HR, Zuo L, et al. CHRM2 gene predisposes to alcohol dependence, drug dependence and affective disorders: results from an extended case-control structured association study. *Hum Mol Genet*. 2005;14(16):2421–2434.
36. Wang JC, Hinrichs AL, Stock H, et al. Evidence of common and specific genetic effects: association of the muscarinic acetylcholine receptor M2 (CHRM2) gene with alcohol dependence and major depressive syndrome. *Hum Mol Genet*. 2004;13(17):1903–1911.
37. Fu Q, Heath AC, Bucholz KK, et al. Shared genetic risk of major depression, alcohol dependence, and marijuana dependence: contribution of antisocial personality disorder in men. *Arch Gen Psychiatry*. 2002;59(12):1125–1132.
38. Ducci F, Goldman D. The genetic basis of addictive disorders. *Psychiatr Clin North Am*. 2012;35(2):495–519.
39. Otten R, van der Zwaluw CS, Engels RC. Testing bidirectional relationships between alcohol use and depressive symptoms: what is the role of the serotonin transporter gene? *Alcohol*. 2018;66:69–75.
40. Dakwar E, Nunes EV, Bisaga A, et al. A comparison of independent depression and substance-induced depression in cannabis-, cocaine-, and opioid-dependent treatment seekers. *Am J Addict*. 2011;20(5):441–446.
41. Boschloo L, Vogelzangs N, van den Brink W, et al. Alcohol use disorders and the course of depressive and anxiety disorders. *Br J Psychiatry*. 2012;200(6):476–484.
42. Jaffee WB, Griffin ML, Gallop R, et al. Depression precipitated by alcohol use in patients with co-occurring bipolar and substance use disorders. *J Clin Psychiatry*. 2009;70(2):171–176.

See supplementary material for this article at PSYCHIATRIST.COM.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

Article Title: Survival Probabilities and Predictors of Major Depressive Episode Incidence Among Individuals With Various Types of Substance Use Disorders

Author(s): Ahmed N. Hassan MD, FRCPC, MPH, and Bernard Le Foll MD, PhD

DOI Number: https://doi.org/10.4088/JCP.20m13637

List of Supplementary Material for the article

1. Table 1 — Univariate analysis of sociodemographic and clinical predictors of a major depressive episode in individuals with substance use disorders

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table 1: Univariate analysis of sociodemographic and clinical predictors of a major depressive episode in individuals with substance use disorders.

Characteristics	Alcohol use disorder (n=5,987) HR (95%CI)	Cannabis use disorder (n=1,353) HR (95%CI)	Opioid use disorder (n=351) HR (95%CI)	Stimulant use disorder (n=827) HR (95%CI)	Nicotine use disorder (n= 3,563) HR (95%CI)
Age at time of interview	**0.96 (0.96-0.97)**	**0.96 (0.95-0.96)**	**0.96 (0.94-0.98)**	**0.96 (0.95-0.98)**	**0.97 (0.96-0.97)**
Substance use disorder age at onset	**0.98 (0.97-0.99)**	**0.96 (0.94-0.99)**	0.98 (0.96-1.01)	0.98 (0.95-1.01)	**0.99 (0.98-0.99)**
Number of use disorder criteria when diagnosed	**1.10 (1.08-1.13)**	**1.14 (1.09-1.20)**	**1.11 (1.02-1.21)**	**1.11 (1.05-1.17)**	**1.17 (1.14-1.21)**
Achieving remission prior to MDE	**0.28 (0.24-0.33)**	**0.23 (0.19-0.28)**	**0.25 (0.15-0.40)**	**0.45 (0.35-0.60)**	**0.29 (0.25-0.33)**
Female	**2.06 (1.77-2.40)**	**1.55 (1.22-1.97)**	1.31 (0.82-2.09)	**1.81 (1.31-2.51)**	**1.94 (1.68-2.25)**
Ethnicity: White	1.06 (0.92-1.21)	1.10 (0.88-1.39)	1.37 (0.89-2.11)	0.81 (0.61-1.09)	0.97 (0.84-1.11)
Marital status:					
Married for the duration of follow up period	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Never married	**1.69 (1.18-2.41)**	2.82 (0.70-11.28)	**2.94 (1.18-7.34)**	**6.78 (2.00-23.01)**	**2.13 (1.61-2.83)**
Other (Separated/divorced or married during follow up)	**2.38 (1.64- 3.46)**	3.62 (0.88-14.84)	**3.82 (1.48-9.97)**	**7.43 (2.06-26.88)**	**1.70 (1.34-2.15)**
Number of weeks unemployed	**1.00 (1.00-1.001)**	1.00 (1.00-1.00)	1.00 (0.99-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Education	0.99 (0.97-1.02)	0.97 (0.92-1.02)	**1.10 (1.00-1.21)**	0.99 (0.93-1.06)	0.99 (0.97-1.02)
Family history of AUD/SUD	**1.65 (1.44-1.88)**	**1.60 (1.30-1.97)**	**2.07 (1.26-3.40)**	**1.72 (1.29-2.31)**	**1.69 (1.48-1.93)**
Family history of MDD	**3.08 (2.61-3.63)**	**2.68 (2.10-3.42)**	**2.81 (1.77-4.46)**	**2.71 (2.01-3.66)**	**2.98 (2.55-3.48)**
Borderline personality disorder	**3.11 (2.69-3.59)**	**2.66 (2.17-3.27)**	**2.19 (1.40-3.42)**	**2.12 (1.63-2.77)**	**3.10 (2.70-3.56)**
Schizotypal personality disorder	**2.75 (2.28-3.31)**	**1.87 (1.42-2.46)**	1.52 (0.87-2.66)	**2.03 (1.44-2.87)**	**2.89 (2.43-3.44)**
Antisocial personality disorder	**2.07 (1.66-2.58)**	**1.72 (1.30-2.28)**	1.21 (0.66-2.23)	**1.62 (1.16-2.26)**	**1.85 (1.52-2.25)**
The presence of one anxiety disorders The presence of two anxiety disorders The presence of three anxiety disorders The presence of four anxiety disorders The presence of five anxiety disorders	**2.63 (2.31-3.00)** **3.70 (3.00-4.57)** **3.62 (2.56-5.13)** **4.14 (2.57-6.67)** **8.59 (5.52-13.37)**	**2.25 (1.79-2.83)** **2.37 (1.70-3.31)** **2.85 (1.86-4.35)** **5.14 (2.41-10.94)** **3.55 (3.06-4.10)**	**1.66 (1.02-2.70)** **2.67 (1.52-4.68)** 1.67 (0.27-10.40) **4.69 (2.05-10.72)** 3.23 (0.31-33.66)	**1.97 (1.45-2.69)** **3.44 (2.28-5.20)** **2.60 (1.19-5.68)** **4.32 (1.74-10.74)** **4.00 (2.92-5.46)**	**2.42 (2.11-2.77)** **3.70 (3.03-4.50)** **4.44 (3.31-5.95)** **3.97 (2.80-5.62)** **7.36 (4.97-10.91)**

Lifetime bipolar disorder	**2.82 (2.21-3.62)**	**2.92 (2.06-4.15)**	1.65 (0.80-3.42)	**3.32 (2.15-5.13)**	**3.04 (2.33-3.98)**
Lifetime PTSD	**2.98 (2.50-3.56)**	**2.39 (1.82-3.14)**	**2.53 (1.59-4.02)**	**2.72 (2.09-3.54)**	**2.82 (2.36-3.37)**
Lifetime alcohol use disorder		1.11 (0.81-1.51)	1.25 (0.72-2.19)	1.14 (0.76-1.72)	1.49 (1.29-1.71)
Lifetime cannabis use disorder	**1.81 (1.54-2.13)**		**1.67 (1.09-2.56)**	1.17 (0.91-1.51)	**1.78 (1.50-2.11)**
Lifetime opioid use disorder	**2.07 (1.71-2.50)**	**1.63 (1.18-2.24)**		1.17 (0.82-1.66)	**1.95 (1.57-2.43)**
Lifetime stimulant use disorder	**0.46 (0.37-0.58)***	1.13 (0.89-1.44)	1.16 (0.80-1.67)		**1.99 (1.58-2.51)**
Lifetime nicotine use disorder	**1.35 (1.20-1.51)**	**1.48 (1.16-1.89)**	1.37 (0.83-2.28)	1.34 (0.93-1.94)	
Childhood adversities	**1.03 (1.02-1.03)**	**1.02 (1.02-1.03)**	1.02 (0.99-1.03)	**1.02 (1.01-1.03)**	**1.02 (1.02-1.03)**

HR: hazard ratio; CI: confidence interval; MDE: major depressive episode; AUD: alcohol use disorder; SUD: substance use disorder; MDD: major depressive disorder; PTSD: post-traumatic stress disorder. [a]: education was evaluated as a continuous variable. *: interaction with time. Bold: statistically significant: $p<0.05$