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The Interaction of Opiate Misuse and Marijuana Use on Behavioral Health Outcomes using the Traumatic Brain Injury Model Systems Pain Collaborative Dataset

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Abstract

Declaration of Interest
The authors have no conflicts of interest.

Objective: To determine if the interaction of opiate misuse and marijuana use frequency is associated with behavioral health outcomes.

Setting: Community

Participants: 3,750 participants enrolled in the TBIMS who completed the Pain Survey and had complete opioid use and marijuana use information

Design: Cross-sectional, secondary analysis from a multi-site observational cohort

Main Outcome Measure(s): Clinically significant behavioral health symptoms for posttraumatic stress disorder (PTSD), depression, anxiety, and sleep quality

Results: 3,535 (94.3%) participants did not misuse opiates, 215 (5.7%) did misuse opiates (taking more opioid pain medication than prescribed and/or using non-prescription opioid pain medication); 2,683 (70.5%) participants did not use marijuana, 353 (9.3%) occasionally used marijuana (less than once a week), and 714 (18.8%) regularly used marijuana (once a week or more frequently). There was a statistically significant relationship ($p<0.05$) between the interaction of opiate misuse and marijuana use frequency and all behavioral health outcomes and several covariates (age, sex, cause of injury, severity of injury, and pain group category). Pairwise comparisons confirm that statistically significant associations on behavioral health outcomes are driven by endorsing opiate misuse and/or regular marijuana use, but occasional marijuana use was not associated.

Conclusions: Higher odds of clinically significant PTSD, depression, anxiety, and poor sleep quality are present in people with TBI who misuse opiates and/or who use marijuana regularly. In the absence of opiate misuse, regular marijuana use had higher odds of worse behavioral health outcomes compared to occasional and no use. The interaction of opiate misuse and regular marijuana use yielded the highest odds. Individuals with TBI should be informed of the relationship of substance use and behavioral health outcomes and that current chronic pain may mediate the association.

Keywords

Traumatic brain injury; Chronic Pain; Marijuana; Opiate; Behavioral Health

Introduction

In 2019, there were more than 223,000 hospitalizations for traumatic brain injury (TBI) in the United States.[1] TBI is often associated with psychological disorders, with approximately 30–61% of adults with moderate-to-severe TBI being diagnosed with a behavioral health condition.[2–4] To illustrate, rates of depression among individuals post-TBI have been reported to range from 19–61%; at-risk substance use from 35–51%; and post-traumatic stress disorder (PTSD) from 27–39%.[2] These negative psychiatric effects can be heightened after multiple TBIs. A prospective cohort study of 586 individuals with TBI found that 35% who experienced multiple TBIs reported illicit drug use, compared to only 15% with no prior history of TBI.[5] They also reported significantly higher rates of anxiety (23% vs. 10%), depression (36% vs. 16%), and sleep disturbance (13% vs. 5%).[5]

Although alcohol use after TBI is well documented,[6–8] there is less information regarding opiate and marijuana use despite clinically-observed high rates for each. Nevertheless, previous studies have consistently indicated that individuals with TBI exhibit significantly elevated rates of opiate misuse and overdose compared to those without TBI.[9–12] Notably, traits such as being male and having a prior history of substance use disorder are associated with occurrence of both TBI and opiate misuse.[13] Individuals with TBI possess a unique combination of clinical and neurobehavioral factors that may explain higher rates of opiate misuse in this population, such as receiving more opiate prescriptions to manage pain and related issues post-TBI, displaying a greater propensity for inappropriate opiate use, and encountering additional challenges in accessing treatment for their substance abuse.[14,15]

In contrast to opiates, the evidence regarding cannabis/marijuana use in individuals with TBI is relatively sparse despite it being the most common drug used by people with TBI who endorse using drugs other than alcohol.[9] The rapidly changing legal environment surrounding marijuana may be contributing to its use, given it is legalized or decriminalized to varying degrees across states, yet remains illegal at the federal level.[9,16] Consequently, to date, no large-scale studies within the United States have been conducted to examine marijuana use post TBI. However, one study in Colorado found that approximately 45% of individuals with TBI (n=64) reported using cannabis, with 31% reporting daily use.[17]

Research into the interaction of opiates and marijuana is even more limited, with some studies reporting improvements in psychosocial outcomes and decreased dependence on opiates among medical marijuana users,[18,19] while others report higher rates of depression and anxiety among users of both.[20,21] Given the prevalence of both opiate and marijuana use and the vulnerability of individuals with TBI to substance misuse and addiction,[2,4,9,10] it is essential to better understand the impact of opiate misuse and marijuana use on outcomes in persons who have incurred a TBI. This study aims to utilize data from the 2018–2023 Traumatic Brain Injury Model Systems (TBIMS) Collaborative study titled *"Characterization and Treatment of Chronic Pain after Traumatic Brain Injury"* to determine if the interaction of opiate misuse and marijuana use is associated with behavioral outcomes, specifically clinically significant depression, anxiety, post-traumatic stress disorder, and sleep quality.

Materials and Methods

Design and Participants

This study analyzed data from the TBIMS Collaborative study titled *"Characterization and Treatment of Chronic Pain after Traumatic Brain Injury"*, sponsored by the National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR). A total of 18 TBIMS collaborating sites contributed to the TBIMS pain collaborative dataset with the goal of examining chronic pain and pain management in survivors of TBI living in the community. Participants enrolled in the TBIMS National Database (which has been consecutively enrolling since 1989) were aged 16 or older at the time of injury, had a history of TBI, and received post-acute rehabilitation care at a participating TBIMS center. During inpatient rehabilitation, participants complete a survey for patient reported outcomes (i.e., demographic and pre-injury information), and clinical data is abstracted from their

medical record. Participants are subsequently followed and given a survey which collects current demographic, medical, psychosocial, and functional outcomes at 1, 2, 5, and each subsequent 5 years post-injury, throughout their lifespan.

For the Collaborative Pain Study, an additional, one-time Pain Survey was delivered within eight weeks of their TBIMS longitudinal follow-up survey (i.e., their usual 1, 2, 5, 10, 15, 20, 25, or 30 year follow-up post injury). Additional eligibility for the Pain Survey required that the TBIMS interview was conducted in English and conducted with the participant (not a proxy). Pain Survey protocols varied slightly based on the participant's pain group category (i.e., Current chronic pain, Past chronic pain (i.e., chronic pain since the TBI but had resolved prior to the Pain Survey), and No chronic pain. The wording of questions was adapted to whether a respondent had indicated they had current, past, or no chronic pain. Respondents who experienced no chronic pain were not administered the chronic pain outcome measures. Note, in this project, we did not examine pain outcome measures, but we utilized current, past, and no chronic pain as a covariate. Data from the standard TBIMS and Pain Survey were joined and made available for analysis. Between May 1st, 2019 and August 31st, 2022, 4,925 participants were eligible to complete the Pain Survey, of which 3,804 were surveyed and included in the final Pain Collaborative dataset.[22]

Main Exposure Measure

The interaction of opiate misuse and marijuana use was the main exposure for this project. A workgroup within the TBIMS Collaborative met to operationalize cut points for opiate misuse and marijuana use based on questions in the Pain Survey.

Opiate history was collected using questions from the Ohio Behavioral Risk Factors Surveillance System survey.[12] Participants who endorsed "Yes" to either of the following two questions were included in the opiate misuse category (i.e., "Opiate Misuse-Yes" or "O_Y"): (1) "The last time you filled a prescription for opioid pain medication, did you use any of the pain medication more frequently or in higher doses than directed by a healthcare provider?" or (2) "In the past year, did you use prescription opioid pain medication that was NOT prescribed to you?" This variable elicited misuse of *prescription* opiate medication and did not include illicit opiate use. Participants who did not endorse either question were included in the no opiate misuse category (i.e., "Opiate Misuse-No" or "O_N").

Marijuana use frequency (i.e., the frequency of using marijuana, cannabis concentrates, and cannabis-infused edibles) was collected in the Pain Survey using questions from the Daily Sessions, Frequency, Age of Onset, and Quantity of Cannabis Use (DFAQ-CU) Inventory.[23] Participants were asked "Which of the following best captures the average frequency you currently use marijuana/cannabis (check one)." Responses included: "I do not use marijuana/cannabis," "less than once a year," "about once a year," "once every 3–6 months (2–4 times per year)," "once every 2 months (6 times per year)," "once a month," "2–3 times per month," "once a week," "twice a week," "3–4 times per week," "5–6 times per week," "once a day," or "more than once a day." The workgroup determined this variable could be trichotomized into three categories – no marijuana use (i.e., "Marijuana-None" or "MJ_N), occasional marijuana use (i.e., "Marijuana-Occasional" or "MJ_O"), defined as between "less than once a year" to "2–3 times per month", and regular marijuana use

(i.e., “Marijuana-Regular” or “MJ_R”), defined as “Once a week” or more frequently. This categorization also has a similar frequency definition to the European Monitoring Centre for Drugs and Drug Addiction which has marijuana frequency categorization cut points of “Once a week or more” or “Less than once a week”.[24]

The interaction of opiate misuse and marijuana use was defined by the combination of opiate misuse (Yes/No) and Marijuana Use (None, Occasional, Regular).

Main Outcome Measures

Behavioral health outcomes for this analysis included clinically significant depressive symptoms (as measured by the Patient Health Questionnaire-9 or “PHQ9”),[25] clinically significant anxiety symptoms (as measured by the General Anxiety Disorder-7 or “GAD7”),[25] clinically significant post-traumatic stress disorder symptoms (as measured by the Post-Traumatic Stress Disorder Checklist for DSM-5 or “PCL5”),[26] and clinically significant sleep quality (as measured by the Pittsburg Sleep Quality Index or “PSQI”).[27] See Table 1 for the definition of the measures and their clinically significant cut-points.

Covariates

Demographic and clinical characteristics from the TBIMS Form I (baseline) and Form II (follow-up) data included age at follow-up (years), sex (Male/ Female), race using 3 “yes”/”no” indicators for White Race, Black Race and Other Race, ethnicity (Hispanic “yes”/”no”), cause of injury (Vehicular/ Violence/ Fall/ Other/ Unknown/Missing), and duration of post traumatic amnesia (PTA) (Mild=One day or less/ Moderate=Greater than one day and less than 7 days/ Severe=Seven days or greater).[28]

Statistical Analysis

The opiate misuse and marijuana use frequency interaction variable was summarized using counts and percentages and stratified by pain group. Covariates and behavioral outcomes were summarized with counts and percentages for categorical variables, means and standard deviations for normally distributed quantitative variables, and medians and interquartile ranges for non-normally distributed quantitative variables and stratified by the opiate misuse and marijuana use frequency interaction variable. Significance testing was performed for covariates to determine if there was statistically significant variation in the distribution of covariates and outcomes between the interaction groups (chi-square tests and cell chi-square for categorical variables, ANOVA for normally distributed quantitative variables, and Kruskal-Wallis for non-normally distributed quantitative variables). Chi-square assumptions were met for all categorical variables (i.e., all variables had expected values of 5 or more in at least 80% of cells). A cut-off of ≥ 2 was used for cell chi-square tests to determine drivers for variation. Effect sizes were calculated for all variables using η^2 derived from ANOVA for normally distributed continuous measures, η^2 derived from Kruskal Wallis for non-normally distributed continuous measures, and Cramer’s V (V) for categorical measures. General linear models were used to test the relationship of the interaction variable on behavioral health outcomes and controlled for age, sex, and pain group. A bar chart was created to depict the percentage (with confidence limits) of the sample who endorsed clinically significant behavioral health outcomes stratified by the opiate misuse

and marijuana frequency interaction variable with a dotted line to depict the average of clinically significant behavioral health outcomes for the full sample. Pairwise contrast statements of the opiate misuse and marijuana frequency variable on behavioral health outcomes (controlling for age, sex, pain group, and the fifteen interaction contrasts) were reported as odds ratios with unadjusted confidence limits; p-values for the 15 pairwise contrasts were assessed for significance using Bonferroni corrections ($\alpha = 0.05/15 = 0.0033$) to demonstrate which interaction terms affected outcomes after controlling for multiple comparisons.

Results

There were 54 participants of the 3,804 in the pain dataset who did not respond to either the opiate misuse or marijuana use variable and were not included in the analysis, yielding a total sample of 3,750 participants. Of these, 3,535 (94.3%) participants did not misuse opiates, 215 (5.7%) did misuse opiates; 2,683 (70.5%) participants did not use marijuana, 353 (9.3%) occasionally used marijuana, and 714 (18.8%) regularly used marijuana. Among the 1,723 participants who reported current chronic pain, 1566 (90.9%) did not misuse opiates, 157 (9.1%) did misuse opiates, 1,139 (66.1%) did not use marijuana, 174 (10.1%) occasionally used marijuana, and 410 (23.8%) regularly used marijuana. Among the 520 participants who reported past chronic pain, 490 (94.2%) did not misuse opiates, 30 (5.8%) did misuse opiates, 390 (75%) did not use marijuana, 51 (9.8%) occasionally used marijuana, and 79 (15.2%) regularly used marijuana. Among the 1,507 participants who reported no chronic pain, 1,479 (98.1%) did not misuse opiates, 28 (1.9%) did misuse opiates, 1,154 (76.6%) did not use marijuana, 128 (8.5%) occasionally used marijuana, and 225 (14.9%) regularly used marijuana. The frequency distribution of the interaction of opiate misuse and marijuana frequency stratified by chronic pain group is shown in Table 2. Significant variation (cell chi square ≥ 2) is shown by an asterisk in cells.

Demographic and clinical characteristics for the sample stratified by the interaction variable are shown in Table 2, demonstrating statistically significant variation with age ($p < 0.001$, $\eta^2 = 0.06$), sex ($p = 0.003$, $V = 0.069$), Black race ($p = 0.018$, $V = 0.061$), cause of injury ($p < 0.001$, $V = 0.077$), severity of injury (as measured by PTA) ($p < 0.001$, $V = 0.079$), and chronic pain group category ($p < 0.001$, $V = 0.128$). Participants in the “Opiate Misuse-No, Marijuana-None” category tended to be older. There was a higher proportion of women in the “Opiate Misuse-No, Marijuana-None” category compared to the other categories, and there was a higher proportion of men in both “Marijuana-Regular” categories (i.e., interaction with both “Opiate Misuse-No” and “Opiate Misuse-Yes”). Asterisks indicate cells that drive the statistical variation for chi-square tests. There was statistically significant variation in the proportion of “Opiate Misuse-No, Marijuana-Regular” for individuals who identify as Black race, and there were no other significant observations with race and ethnicity.

Behavioral outcomes stratified by the opiate misuse and marijuana frequency interaction variable are summarized in Table 3. There was statistically significant variation across all outcomes [PCL5 ($p < 0.001$, $V = 0.165$), PHQ9 ($p < 0.001$, $V = 0.154$), GAD7 ($p < 0.001$, $V = 0.164$), and PSQI ($p < 0.001$, $V = 0.144$)] which is also depicted in Figure 1. People

who misused opiates or who were regular marijuana users were more likely to have worse clinically significant behavioral health outcomes compared to people who did not misuse opiates and did not use marijuana. People in the “Opiate Misuse-No, Marijuana-Occasional” group did not manifest worse clinically significant behavioral health symptoms, and were similar to the “Opiate Misuse-No, Marijuana-None” group when compared to the other interaction groups. Pairwise comparisons of the opiate misuse and marijuana frequency interaction variable on behavioral outcomes are reported in Table 4 and confirm that the statistically significant associations are largely driven by endorsing opiate misuse, with increased effect among individuals who also endorsed regular marijuana use.

Discussion

This cross-sectional analysis of the TBIMS Chronic Pain Collaborative dataset showed worse behavioral health outcomes among people who reported misusing opiates or using marijuana regularly (i.e., once a week or more). The distribution of the interaction response categories yielded an adequate sample size to make meaningful associations with behavioral health outcomes. Opiate misuse and regular marijuana use was more frequent in those with current chronic pain compared to those with past chronic pain and no chronic pain, indicating that current pain may be associated with using these substances. Overall, our sample demonstrated a higher prevalence of marijuana use than opiate misuse. Although no causality can be inferred, this finding suggests that marijuana use in this sample may have a reciprocal relationship with opiate misuse, which would align with previous work demonstrating this relationship.[29,30]

Demographic and clinical characteristics across the opiate misuse and marijuana use categories showed significant variation across age, sex, cause of injury, severity of injury, and pain group category. Participants who reported opiate misuse and any marijuana use tended to be younger, and regular marijuana users tended to be men. These observations are consistent with current trends in the United States general population where the highest percentage of active opiate misuse and marijuana use are among people aged 18 to 25 years,[23,31,32] with men reporting cannabis use more frequently than women. The proportion of falls as cause of injury was higher among the “Opiate Misuse-No, Marijuana-None” category, which may be related to that group’s older age. This observation aligns with previous data that shows that older individuals are more likely to have sustained a fall as their cause of injury compared to younger individuals.[33]

In general, increased odds for worse behavioral health outcomes were associated with opiate misuse regardless of marijuana frequency after controlling for age, sex and chronic pain group category. Increased odds were only associated with marijuana frequency among individuals who endorsed regular marijuana use versus no marijuana use within those who did not endorse opiate misuse. Further, endorsing both opiate misuse and regular marijuana use resulted in the largest odds for worse behavioral health outcomes. These associations align with previous research showing that opiate misuse or marijuana use are associated with higher rates of PTSD, depression, anxiety, and poorer sleep quality.[34,35] However, no prior studies have examined the interaction of opiate misuse and marijuana frequency in the context of TBI; nor have previous studies divided marijuana use into frequency categories.

Using this approach, we found that individuals who misuse opiates and/or regularly use marijuana drive the associations with worse behavioral health outcomes, but occasional marijuana use was not associated with worse outcomes.

Though causality cannot be determined from this study, it is important to consider these findings given the known side effects of opiates and marijuana,[36–38] and the potential impact on individuals with TBI living in the community.[9,10,39,40] The additional vulnerability that may arise from use of these substances seems especially salient given that individuals with TBI are already at risk for poor behavioral health outcomes.[41,42] Further, depression and anxiety have been associated with early exposure to marijuana in adolescents,[43] and screening for substance use history and current use should be routine practice.

There has been conflicting evidence regarding the efficacy of marijuana to treat depression, PTSD, anxiety, and sleep deprivation.[44–46] Recently published clinical practice guidelines reviewed literature investigating the use of cannabinoid-based medicines (CBM) for treatment of chronic pain in co-occurring conditions.[47] These guidelines strongly recommended CBM adjunct therapy for sleep deprivation and anxiety among people who experience chronic pain, and weakly recommended CBM adjunct therapy for PTSD and depression.[47] Further, a strong recommendation for CBM adjunct therapy was endorsed for opioid sparing for people who use opioids for chronic pain.[47] These recommendations were not specific to individuals with TBI. Future longitudinal research investigating CBM adjunct therapy among individuals with TBI will be important to determine if similar benefits exist or if those benefits outweigh the potential risks of increased behavioral health symptoms identified in the current study.

Study Limitations

Given the cross-sectional design of this study, no causal associations may be inferred. The methodology is prone to recall bias (i.e., recalling past experiences and reduced insight and/or memory associated with having a TBI) and social desirability bias (i.e., hesitation to report socially unfavorable responses). The information available for analysis is limited to the questions asked in the survey. Despite a relatively small percentage of individuals endorsing opiate misuse, statically relevant associations were present. The opiate misuse variable questions had different anchors of time (i.e., no time reference for using opiates more frequently than prescribed versus “In the past year” for using opiates not prescribed), which may have changed the way people responded to the questions. Further, onset and cessation of chronic pain were not collected; dosages of opiate or marijuana were not collected; opiate use outside of prescription medications was not collected. The marijuana use variable only describes frequency of use, and no questions were asked pertaining to dosage, prescription, legality, or route of administration. A future analysis is warranted to understand state variation pertaining to cannabis legality and frequency of marijuana use on outcomes. Generalizability may be limited to people with TBI who received inpatient rehabilitation, speak English, and who completed the survey without a proxy.[22,48] Further, while the TBIMS sample has been established to be largely representative of the population of adults admitted for acute, inpatient rehabilitation in the US with a primary diagnosis of TBI, the TBIMS tends to include participants with overall younger age at time of injury,

higher employment rates at injury (and lower retirement rates), and longer rehabilitation length of stays.[49] In addition, participants who completed the Pain Survey tended to be younger at follow-up, had higher levels of education, were less likely to abstain from alcohol and more likely to be light drinkers, and tended to have better functional outcomes on the DRS and GOS-E as compared to TBIMS participants who were eligible but did not complete the pain survey, although associated effect sizes were small (Harrison-Felix et al. 2023, under review).[22] These differences may affect the generalizability of our results to the larger TBI population. Finally, pain outcomes were not explored in the current study because only individuals who endorsed chronic pain were asked pain outcomes, thus future research could examine the association of marijuana and opiate use on pain outcomes among participants who endorsed chronic pain.

Conclusion

This study demonstrated higher odds of clinically significant PTSD, depression, anxiety, and poor sleep quality in individuals with TBI who misuse opiates and/or regularly use marijuana. In the absence of opiate misuse, those who endorsed regular marijuana use had higher odds of worse behavioral health outcomes compared to occasional and no use. The interaction of opiate misuse and regular marijuana use yielded the highest odds. Although a causal relationship between these substances and outcomes cannot be made based on study methodology, providers should inform individuals with a history of TBI of the association of use and behavioral health outcomes and that current chronic pain may mediate the association. Further research is warranted to guide clinical recommendations of adjunct CBM therapy for individuals with TBI.

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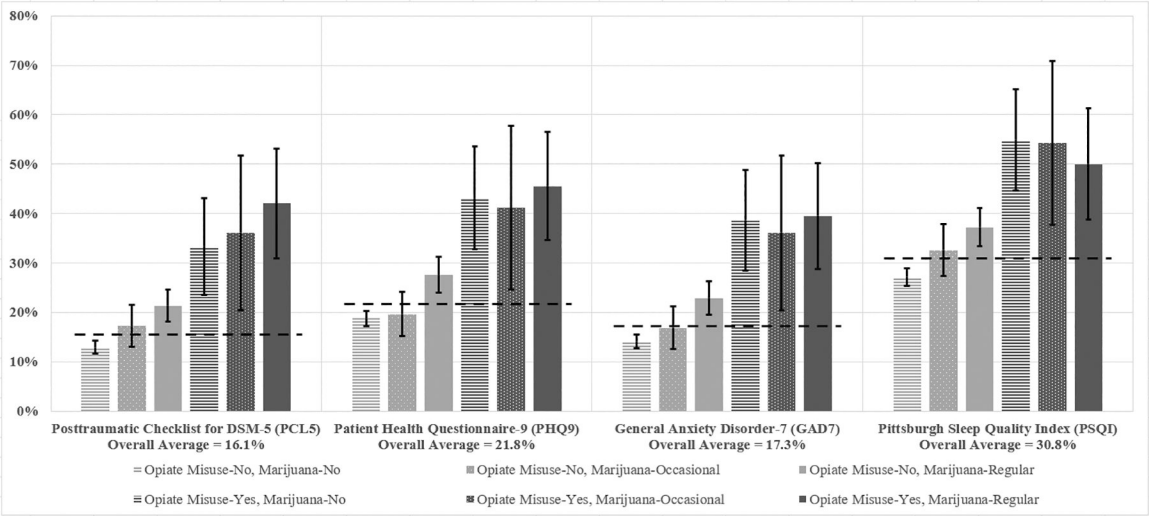

Figure 1.

Clinically Significant Behavioral Health Outcomes stratified by opiate misuse and marijuana frequency interaction variable with confidence limits and overall average depicted

Table 1.

Behavioral Health Outcomes with definition and clinically significant cut points

Behavioral Health Outcome	Definition	Clinically significant cut point
Patient Health Questionnaire-9 (PHQ-9)	Patient Health Questionnaire-9 (PHQ-9) is a 9-item questionnaire used for screening for depressive symptoms. Scores range from 0 to 27 with a score of 5, 10, 15, and 20 representing mild, moderate, moderately severe, and severe depressive symptoms, respectively. Scores greater than 10 have been suggested to be clinically significant. This survey has been used in the general and traumatic brain injury population for screening for major depressive disorder.	≥ 10
Generalized Anxiety Disorder-7 (GAD-7)	Generalized Anxiety Disorder-7 (GAD-7) has 7 items correlated with cognitive, somatic, and emotional symptoms related to the diagnosis of anxiety and can aid in grading severity. Scores range from 0 to 21 with scores of 5, 10, and 15 represent mild, moderate, and severe anxiety symptoms, respectively. Scores greater than 8 have been suggested to be clinically significant. This form has been validated and applied in the general and traumatic brain injury population.	≥ 10
Post-Traumatic Stress Disorder Checklist for DSM-5 (PCL-5)	Post-Traumatic Stress Disorder Checklist for DSM-5 (PCL-5) is a revision to the initial Post-traumatic Stress Disorder Checklist (PCL) to reflect changes to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) diagnostic criteria of PTSD. The survey consists of 20 items graded on total point of 0 to 80, with scores greater than or equal to 33 are associated with diagnosis of PTSD. It has been widely used and shown to have good reliability in general and military population – with and without history of traumatic brain injury.	≥ 33
Pittsburgh Sleep Quality Index (PSQI)	Pittsburgh Sleep Quality Index (PSQI) was developed to assess sleep quality over a 1-month time interval, scores ranging from 0 to 21. Scores greater than 8 indicate a higher risk for poor sleep and insomnia. This survey also used in TBI population.	≥ 9

Table 2.

Demographic and clinical characteristics of sample stratified by the opiate misuse and marijuana frequency interaction variable

	O_NMJ_N (N = 2590)		O_NMJ_O (N = 314)		O_NMJ_R (N = 631)		O_YMJ_N (N = 93)		O_YMJ_O (N = 39)		O_YMJ_R (N = 83)			
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p-value**	**Effect Size**
Age at follow up	49.4	16.8	42.3	14.0	40.3	13.5	42.8	12.8	40.3	12.0	39.4	12.8	**<0.001**	**0.06**
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**		
Years post-injury	5.4	2.0, 14.6	5.5	2.1, 14.6	5.5	2.1, 14.7	5.1	1.9, 14.6	9.8	4.6, 15.0	5.5	2.1, 14.6	0.578	<0.001
	Count	**Percent**	**Count**	**Percent**	**Count**	**Percent**	**Count**	**Percent**	**Count**	**Percent**	**Count**	**Percent**		
Sex													**0.003**≠	**0.069**
Male	1881	72.7%	236	75.2%	503	79.7% *	71	76.3%	28	71.8%	69	84.2% *		
Female	708	27.3% *	78	24.8%	128	20.3% *	22	23.7%	11	28.2%	13	15.8% *		
Unknown/Missing	1	<0.1%	0	0%	0	0%	0	0%	0	0%	0	0%		
Race														
White Race†	1969	76.2%	243	77.6%	477	76.1%	74	80.4%	37	94.9%	59	72.0%	0.091≠	0.050
Black Race†	449	17.4%	54	17.3%	127	20.3%*	11	12.0%	0	0% *	16	19.5%	**0.018**≠	**0.061**
Other Race†	167	6.5%	20	6.4%	31	4.9%	5	5.4%	1	2.6%	7	8.5%	0.579≠	0.032
Hispanic Ethnicity†	279	10.8%	35	11.2%	67	10.6%	9	9.7%	5	12.8%	9	11.0%	0.997≠	0.009
Cause of Injury													**<0.001**≠	**0.077**
Vehicular	1326	51.2% *	183	58.3%	375	59.4% *	49	52.7%	23	59.0%	44	53.0%		
Violence	293	11.3%	33	10.5%	78	12.4%	19	20.4% *	9	23.1%	10	12.0%		
Fall	682	26.3% *	64	20.4%	89	14.1% *	12	12.9% *	5	12.8%	15	18.1%		
Other	287	11.0%	33	10.5%	85	13.6% *	13	14.0%	2	5.1%	13	15.9%		
Unknown/ Missing	2	0.1%	1	0.3%	4	0.6%	0	0%	0	0%	1	1.2%		
Severity of Injury (Post Traumatic Amnesia)													**<0.001**≠	**0.079**
Mild (≤1 day)	370	14.3% *	35	11.2%	43	6.8% *	13	14.0%	4	10.3%	8	9.6%		
Moderate (1–7 days)	345	13.3%	33	10.5% *	86	13.6%	11	11.8%	6	15.4%	11	13.3%		

	O_NMJ_N (N = 2590)		O_NMJ_O (N = 314)		O_NMJ_R (N = 631)		O_YMJ_N (N = 93)		O_YMJ_O (N = 39)		O_YMJ_R (N = 83)			
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p-value**	**Effect Size**
Severe (>7 days)	1459	56.3% *	211	67.2%	436	69.1% *	56	60.2%	21	53.9%	55	66.3%		
Unknown/ Missing	416	16.1%	35	11.2%	66	10.5%	13	14.0%	8	20.5%	9	10.8%		
Chronic Pain Group													**<0.001**	**0.128**
Current chronic pain	1070	41.3% *	145	46.2%	351	55.6% *	69	74.2% *	29	74.4% *	59	71.1% *		
Past chronic pain	376	14.5%	45	14.3%	69	10.9% *	14	15.1%	6	15.4%	10	16.9%		
No chronic pain	1144	44.2% *	124	39.5%	211	33.4% *	10	10.8% *	4	10.3% *	14	12.1% *		

Interaction definitions: O_NMJ_N = Opiate Misuse-No, Marijuana-None; O_NMJ_O = Opiate Misuse-No, Marijuana-Occasional; O_NMJ_R = Opiate Misuse-No, Marijuana-Regular; O_YMJ_N = Opiate Misuse-Yes, Marijuana-None; O_YMJ_O = Opiate Misuse-Yes, Marijuana-Occasional; O_YMJ_R = Opiate Misuse-Yes, Marijuana-Regular

†Participants may self-report more than one race;

$^{\neq}$Removed 'Unknown/Missing' for Chi-Square Calculations;

*Cell chi-square > 2

Effect size η^2 derived from ANOVA model for age at follow up where 0.01, 0.06, and 0.14 represent small, medium, and large effect sizes, respectively

Effect size η^2 derived from Kruskal-Wallis test for years post-injury test where 0.01, 0.06, 0.14 represent small, medium, and large effect sizes, respectively

Effect size from Cramer's V (*V*) derived from chi-square test when df = 1 (sex, white race, black race, other race, and Hispanic ethnicity) where 0.1, 0.3, and 0.5 represent small, medium, and large effect sizes, respectively; when df = 2 (severity of injury and chronic pain group) where 0.07, 0.21, and 0.35 represent small, medium, and large effect sizes, respectively; and when df = 3 (cause of injury) where 0.06, 0.17, and 0.29 represent small, medium, and large effect sizes, respectively.

Table 3.

Behavioral characteristics stratified by the opiate misuse and marijuana frequency interaction variable

	O_NMJ_N (N = 2590)		O_NMJ_O (N = 314)		O_NMJ_R (N = 631)		O_YMJ_N (N = 93)		O_YMJ_O (N = 39)		O_YMJ_R (N = 83)			
Category	**Count**	**Percent**	**Count**	**Percent**	**Count**	**Percent**	**Count**	**Percent**	**Count**	**Percent**	**Count**	**Percent**	**p-value**	**Effect size**
Posttraumatic Checklist for DSM-5 (PCL5) (Cut point ≥ 33)													**<0.001** ≠	**0.165**
No	2211	85.4% *	254	80.9%	483	76.5% *	60	64.5% *	23	59.0%	44	53.0% *		
Yes	329	12.7% *	53	16.9%	131	20.8% *	30	32.3% *	13	33.3% *	32	38.6% *		
Unknown/ Missing	50	1.9%	7	2.2%	17	2.7%	3	3.2%	3	7.7%	7	8.4%		
Patient Health Questionnaire-9 (PHQ9) (Cut point ≥ 10)													**<0.001** ≠	**0.154**
No	1954	75.4% *	241	76.8%	430	68.1% *	50	53.8% *	20	51.3%	43	51.8% *		
Yes	452	17.5% *	59	18.8%	164	26.0% *	38	40.9% *	14	35.9% *	36	43.4% *		
Unknown/ Missing	184	7.1%	14	4.5%	37	5.9%	5	5.4%	5	12.8%	4	4.8%		
General Anxiety Disorder-7 (GAD7) (Cut point ≥ 10)													**<0.001** ≠	**0.164**
No	2067	79.8% *	246	78.3%	454	71.9% *	54	58.1% *	23	59.0%	49	59.0% *		
Yes	341	13.2% *	50	15.9%	135	21.4% *	34	36.3% *	13	33.3% *	32	38.6% *		
Unknown/ Missing	182	7.0%	18	5.7%	42	6.7%	5	5.4%	3	7.7%	2	8.4%		
Pittsburgh Sleep Quality Index (PSQI) (Cut point ≥ 9)													**<0.001** ≠	**0.144**
No	1827	70.5% *	207	65.9%	381	60.4% *	41	44.1% *	16	41.0% *	38	45.8% *		
Yes	682	26.3% *	100	31.8%	226	35.8% *	50	53.8% *	19	48.7% *	38	45.8% *		
Unknown/ Missing	81	3.1%	7	2.2%	24	3.8%	2	2.2%	4	10.3%	7	8.4%		

Interaction definitions: O_NMJ_N = Opiate Misuse-No, Marijuana-None; O_NMJ_O = Opiate Misuse-No, Marijuana-Occasional; O_NMJ_R = Opiate Misuse-No, Marijuana-Regular; O_YMJ_N = Opiate Misuse-Yes, Marijuana-None; O_YMJ_O = Opiate Misuse-Yes, Marijuana-Occasional; O_YMJ_R = Opiate Misuse-Yes, Marijuana-Regular

Clinical Significance cut-offs: PCL5 ≥ 33; PHQ9 ≥ 10; GAD7 ≥ 10; PSQI ≥ 9

≠ Removed 'Unknown/Missing' for Chi-Square Calculations;

* Cell chi-square > 2

Effect size from Cramer's V (*V*) derived from chi-square test when df = 1 (PCL5, PHQ9, GAD7, and PSQI) where 0.1, 0.3, and 0.5 represent small, medium, and large effect sizes, respectively

Table 4.

Pairwise comparisons of opiate misuse and marijuana frequency variable on behavioral health outcomes reported as adjusted odds ratios and confidence limits

		Post-Traumatic Stress Disorder Checklist-5	Patient Health Questionnaire-9	General Anxiety Disorder-7	Pittsburg Sleep Quality Index
Interaction Group 1 vs	**Interaction Group 2**	**OR (LCL, UCL)**	**OR (LCL, UCL)**	**OR (LCL, UCL)**	**OR (LCL, UCL)**
Opiate Misuse = No					
O_NMJ_R	O_NMJ_N	**1.31 (1.03, 1.67)**	**1.27 (1.01, 1.58)**	**1.33 (1.05, 1.69)**	**1.29 (1.06, 1.59)**
O_NMJ_O	O_NMJ_N	1.18 (0.84, 1.64)	0.91 (0.66, 1.25)	1.03 (0.73, 1.44)	1.19 (0.90, 1.56)
O_NMJ_R	O_NMJ_O	1.12 (0.77, 1.62)	1.39 (0.98, 1.98)	1.29 (0.89, 1.88)	1.09 (0.80, 1.48)
Opiate Misuse = Yes					
O_YMJ_R	O_YMJ_N	1.49 (0.77, 2.90)	1.08 (0.57, 2.05)	1.05 (0.55, 2.02)	0.86 (0.46, 1.64)
O_YMJ_O	O_YMJ_N	1.06 (0.45, 2.47)	0.91 (0.39, 2.11)	0.85 (0.37, 1.97)	0.99 (0.44, 2.24)
O_YMJ_R	O_YMJ_O	1.41 (0.60, 3.33)	1.18 (0.51, 2.77)	1.24 (0.53, 2.90)	0.87 (0.38, 2.02)
MJ Use = Never					
O_YMJ_N	O_NMJ_N	**2.05 (1.28, 3.30)** *	**2.13 (1.35, 3.36)** *	**2.43 (1.53, 3.87)** *	**2.10 (1.35, 3.28)** *
MJ Use = Occasional					
O_YMJ_O	O_NMJ_O	1.85 (0.85, 4.02)	2.13 (0.98, 4.62)	2.02 (0.93, 4.39)	1.75 (0.84, 3.68)
MJ Use = Regular					
O_YMJ_R	O_NMJ_R	**2.33 (1.38, 3.94)** *	**1.81 (1.10, 2.99)**	**1.93 (1.16, 3.22)**	1.40 (0.85, 2.32)
Other Contrasts					
O_YMJ_R	O_NMJ_N	**3.07 (1.86, 5.06)** *	**2.30 (1.42, 3.71)** *	**2.56 (1.58, 4.17)** *	**1.82 (1.12, 2.95)**
O_YMJ_R	O_NMJ_O	**2.61 (1.47, 4.63)** *	**2.52 (1.45, 4.38)** *	**2.50 (1.42, 4.40)** *	1.53 (0.89, 2.62)
O_YMJ_O	O_NMJ_R	1.66 (0.79, 3.47)	1.53 (0.73, 3.20)	1.56 (0.75, 3.26)	1.61 (0.79, 3.30)
O_YMJ_O	O_NMJ_N	**2.17 (1.05, 4.49)**	1.94 (0.94, 4.00)	**2.07 (1.01, 4.26)**	**2.08 (1.03, 4.21)**
O_YMJ_N	O_NMJ_R	1.56 (0.95, 2.58)	**1.68 (1.04, 2.72)**	**1.83 (1.12, 3.00)**	**1.63 (1.02, 2.59)**
O_YMJ_N	O_NMJ_O	**1.75 (1.00, 3.03)**	**2.34 (1.37, 3.98)** *	**2.37 (1.37, 4.10)** *	**1.77 (1.07, 2.93)**

Interaction definitions: O_NMJ_N = Opiate Misuse-No, Marijuana-None; O_NMJ_O = Opiate Misuse-No, Marijuana-Occasional; O_NMJ_R = Opiate Misuse-No, Marijuana-Regular; O_YMJ_N = Opiate Misuse-Yes, Marijuana-None; O_YMJ_O = Opiate Misuse-Yes, Marijuana-Occasional; O_YMJ_R = Opiate Misuse-Yes, Marijuana-Regular

OR=Odds Ratio; LCL=Lower Confidence Limit; UCL=Upper Confidence Limit

Statistically significant odds ratios and confidence intervals are bolded

* Statistical significance at the Bonferroni p-value (p=0.0033)

Effect size from Odds Ratios where 1.68, 3.47, and 6.71 represent small, medium, and large effect sizes, respectively

All models converged and were adjusted for age, sex, and pain group.