UNIVERSITY OF CALIFORNIA,
IRVINE

The Prevalence and characteristics of patients with marijuana exposure at the time of injury in moderate or severe traumatic brain injury: A retrospective observational cross-sectional study

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in Nursing Science

by

Dina Elias

Dissertation Committee:
Professor Miriam Bender, Chair
Professor David Holmes
Professor Sanghyuk Shin

2021

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I would like to express my sincerest gratitude to my committee chair, advisor and mentor Professor Miriam Bender, who has the attitude and the substance of a brilliant intellect; she continually and compellingly conveyed a spirit of adventure and excitement in regard to scholarship and research. Without her guidance and persistent help this dissertation would not have been possible.

I would like to thank my committee members, Professor S. Shin and Professor D. Holmes, whose support and expert advice were invaluable throughout my scholarly journey. They provided mentorship, constructive feedback and guidance that helped shape my research and journey of learning.

Finally, this dissertation would not have been possible without the love, support, and encouragement I received from my parents, my husband, my siblings and their families. To all my friends, thank you for the constant motivation. To all of you, I wanted to say thank you for always being available to hear me rant, for calming my anxieties, and for providing constant assurance that all will be well.

VITA

OBJECTIVE

As a registered nurse, my objective is to provide the best possible holistic care to each of my patients. I am a firm believer in the process of self-learning and grasp all learning opportunities offered to me. Throughout my journey, I hope to grow, not just as a professional nurse, but also as a person who empowers, comforts, and supports her patients through their own journey of healing.

EXPERIENCE

September 2017 – Present Riverside Community Hospital

Trauma Program Director

- Provides 24 hour administrative and educational oversight for the Trauma Service Program to include organizing, developing, directing, and assuring the delivery of cost-effective, quality patient care. Supervises and manages 11 staff members of the program: 5 Registered Nurses, 5 Trauma Registrars, 1 Program Assistant.
- Supervises 11 staff members, including registered nurses and trauma registrars.
- Plans, organizes and leads the components, scope and implementation of nursing practice for achievement of both short and long-term goals for the hospital as well as the entire health care corporation in collaboration with other disciplines and services.
- Determines the organizational structure, clinical operations, standards and practices, and makes revisions consistent with changing legal, regulatory and hospital wide verification requirements.
- Directs the preparation of budget for the trauma program; integrates with organizational and corporate budge while justifying both personnel and program resource requests.
- Evaluates and directs corrective actions regarding trauma program operational compliance with verification, accreditation and regulatory standards.
- Evaluates the performance of trauma program staff; addresses and resolves problems and issues involving grievances and disciplinary action.
- Analyzes trauma data, researches issues and works with trauma team to develop immediate and long-range solutions especially as it relates to trauma program performance improvement opportunities.
- Directs the entry of statistics and data into the trauma registry. Identifies trends and provides follow-up.

- Assists in selection of trauma charts for Quality Improvement and Assurance monitoring; leads and engages key stakeholders to ensure the implementation of quality improvement activities.
- Coordinates ancillary services to ensure a comprehensive multi-disciplinary approach to trauma care.
- Promotes paitent and family advocacy.
- Coordinates nursing aspects of trauma program with appropriate hospital directors and senior leadership to champion patient safety efforts and reduce facility risks.
- Participates and directs the planning, developing, organizing, and evaluation of the trauma program.
- Formulates policies, procedures, practice management guidelines and standards of care practices for the trauma program as well as the organization and nursing departments.
- Supervises and evaluates performance of all trauma team members, identifying areas needing improvement both in individual and team functions.
- Provides guidance, counseling, advice to supervising nurses on techniques of staff supervision, patient care planning, problem solving, policies, and methods of performing Nursing procedures.
- Responsible for formal and informal teaching programs related to trauma care and/or trauma skills.
- Supervises trauma team members' orientation and clinical practice.
- Determines need for education and training to improve clinical practice as it relates to trauma and critical care nursing practice.
- Develops ongoing education to trauma nurses in the emergency department, critical care units and medical-surgical units, some of the courses are listed below:
    - Trauma care across the continuum course
    - Orientation to new trauma nurses in the emergency department
    - Introduction to trauma and critical care concepts to new intensive care unit nurses
- Maintains current knowledge of trauma care and serves as an expert clinician to nursing staff and hospital leadership regarding trauma critical care knowledge and practice.
- Participates in direct care to assess clinical skills and serve as a clinical resource for nursing staff and other hospital units.
- Assists in identification of new equipment and evaluation.
- Participates in community education.

May 2015 – September 2017 Riverside Community Hospital

Trauma Clinical Nurse Specialist

- Functions as expert practitioner, educator, consultant, and researcher with the proportion of time spent in each subrole based on the needs of the trauma program.
- Demonstrates clinical nursing expertise in diagnosing and treating patients with complex trauma related conditions.
- Advances the practice of nursing by designing evidence-based interventions and influencing the practice of other nurses within the hospital system to enhance and support autonomous nursing practice.
- Responsible in providing nursing education in clinical and didactic settings.
- Responsible for coordinating educational classes, rounds, clinical rounds and in-services, as well as training and evaluating new trauma nurses.

December 2013 – May 2015 Harbor-UCLA Medical Center

Clinical Nurse Specialist – Pediatric Critical Care

- Provide education and support to staff nurses regarding implementation of evidenced-based practices and new technologies

August 2011 – May 2015 Harbor - UCLA Medical Center

Clinical Nurse Specialist – Trauma/Surgical Critical Care

- Provide evidence-based nursing care to patients, their families, and nursing staff in highly complex clinical situations through education, consultation, leadership, clinical expertise and direct care, and collaboration with various members of the healthcare team.
- Provide clinical support and acts as a consultant and resources to staff members and members of the healthcare team to ensure standards of care are achieved.
- Assist in quality improvement of 14 bed Surgical/Trauma ICU and 6 bed Cardiothoracic ICU, including collaborating with team members in the institution of Ventilator Associated Pneumonia and Central Line Associated Blood Stream Infection bundles. Championed order sets in collaboration with other healthcare team members through committee approval to improve patient care and Joint Commission compliance.
- Provide expert consultation and experience in the development of evidence-based policies and procedures for the Department of Nursing.
- Developed the Progressive Mobility Protocol for the adult intensive care units for Harbor UCLA, and the protocol is now used to help other DHS hospitals develop their own program for progressive mobility. Held multiple classes to educate all adult intensive care unit nurses. Gathering data on VAPs, falls, pressure ulcer development, and length of stay in the ICU as measurable outcomes.

- Coordinate and provide ongoing instruction for Continuous Renal Replacement Therapy classes. Currently coordinating classes to transition from Prisma to Prisma Flex machines.
- Coordinate inservices and educational forums for nursing staff based on identified educational needs.
    - Inservices provided (2012-current):
        - Klebsiella Pneumonia Infection Control
        - Medication Safety: Chemotherapy Agents DHS System Wide Fall Prevention Program Precedex (March 2012)
        - Malnutrition Screening
        - IV Therapy Policy Revisions
        - Procedural Sedation
        - Intraperitoneal chemotherapy
        - Heparin Infusion Protocol
        - PCA Practice Changes
        - New Flexiseal Drainage System
        - Weaning Protocol: Vent Patients
        - Critical care pain observation tool
        - CERNER Electronic Medical Record System Super User Trainer
- Assist in the annual training of nursing staff by developing testing and teaching stations for the Department of Health Services Annual Competency Testing, as well as the in-house Skills Assessment Workshop. Developed and coordinated critical care "skills sharpener" for all the ICU's.
- Assist with training and educational classes to ensure maintenance and advancement of clinical skills, including but not limited to:
    - Classes taught in the past year:
        - Adult ICU Class: the basics
        - Progressive Mobility in the ICU
        - Lab Interpretation
        - ABG Interpretation
        - Basic EKG Interpretation
        - Mechanical Ventilator Basics
        - Identifying Clinical Cues in the deteriorating patient
        - Electrolytes
        - Continuous Renal Replacement Therapy
        - CCRN: Critical Care Nursing Certification review class
- Select topics and promote speaker involvement and development for nursing grand rounds as assigned by department supervisor

- Perform weekly teaching rounds with ICU staff:
    - Topics include but not limited to:
        - EKG Rhythm: NSR with Ventricular Quadrigemeny
        - Abdominal Compartment Syndrome
        - Preventing Ventilator Associated Pneumonia
        - Effects of immobility/Progressive Immobility
        - Hepatic Encephalopathy
        - Removal of the EZ-IO
        - Ventriculostomies and management
        - Hypothermia Protocol
        - Insertion and removal of a Pulmonary Artery Catheter
        - Coordination of care
        - Ludwig's Angina
- Contribute authored/written sections for publishing in the Orientation/Reorientation manual for Harbor-UCLA Medical Center annual orientation competency.
    - Sections authored and/or reviewed:
        - Understanding Sepsis and its implications
        - Patient Care Management: Ergonomics, Pain Management, Organ and Tissue Donation
        - Infection Control
        - Environment of Care Issues: Fire/Life Safety, Emergency preparedness, Hazardous Materials Communication and Safety Program
- Assist with new staff orientation to the critical care unit, monitoring their progress weekly by meeting with preceptor and staff and providing ongoing education support.
- Co-Chair of the Clinical Practice Council
- Lead CNS for revisions of Nursing Policies, as well as Critical Care Specialty Manuals
- Facilitate patient care by ensuring appropriate resources are identified and utilized to attain best outcome measures for the patient throughout the continuum of care.
- Assess and aid in the ongoing quality improvement of patient care and patient care outcomes.
- Ensure ongoing training regarding state mandates and preparation for The Joint Commission visits.
- Coordinator and instructor for in hospital CCRN review class.
- Coordinator and instructor for 2013 unit-based ICU skills fair.

- Coordinator of ICU Educational teaching rounds that occur once a month and taught by various practitioners.
- Chair of surgical intensive unit critical care sub-committee.
- Instructor, champion and coach for TeamSTEPPS implementation on the unit level and hospital wide implementation.
- Facilitator and coordinator for Proning Protocol in Medical ICU. Developed and created order sets and practice protocol.
- Co-champion weekly Multidisciplinary Rounds addressing evidence-based quality initiatives for critical care.

May 2011 – August 2013 UCLA Graduate School of Nursing

Clinical Faculty – Acute Care NP/CNS Program

- Supervise student groups in clinical areas. When students are precepted, meets with preceptor and student periodically. Is available during clinical time.
- Responsible, along with other clinical faculty, for producing and distributing course learning objectives and course syllabus.
- Evaluate and grade student performance. Meets with students at midterm for formal evaluation and again at the end of the course. Files final evaluation with Student Affairs Office.
- Maintain faculty expectations as required by the School of Nursing.

Oct 2010 – August 2011 Orange Coast Memorial Hospital

Clinical Nurse Specialist – Critical Care

- Provide evidence-based nursing care to patients, their families, and nursing staff in highly complex clinical situations through education, consultation, leadership, clinical expertise and direct care, and collaboration with various members of the healthcare team.
- Provide clinical support and acts as a consultant and resources to staff members and members of the healthcare team to ensure standards of care are achieved.
- Coordinate inservices and educational forums for nursing staff based on identified educational needs.
- Assist with training and educational classes to ensure maintenance and advancement of clinical skills.
- Assist with new staff orientation to the critical care unit, monitoring their progress weekly by meeting with preceptor and staff and providing ongoing education support.
- Facilitate patient care by ensuring appropriate resources are identified and utilized to attain best outcome measures for the patient throughout the continuum of care.

- Assess and aid in the ongoing quality improvement of patient care and patient care outcomes.
- Ensure ongoing training regarding state mandates and preparation for The Joint Commission visits.

August 2004 – Oct 2010 Harbor-UCLA Medical Center

Clinical Nurse Educator – Trauma/Surgical Critical Care

- Responsible for Trauma and Surgical Intensive Care Unit, Cardiothoracic Intensive Care Unit, Step-down and Medical-Surgical unit service line.
- Responsible in providing nursing education in clinical and didactic settings. Responsible for coordinating educational classes, grand rounds, clinical rounds and in-services, as well as training and evaluating new orientees.
- Aid in the preparation of nursing personnel for JCAHO accreditation, as well as instituting new nursing policies and revising existing ones.
- Work collaboratively with the Nurse Manager, physicians, and nursing staff in maintaining professional clinical practice.
- Work closely with interdisciplinary health care team in developing plans of care for patients in the surgical intensive care unit.

January 2004 – June 2004 Oakland Community College, MI

Lab Instructor

- Taught a physical assessment lab and open lab for first year students.

May 2003 – June 2004 Oakland Community College, MI

Clinical Instructor

- Taught a group of 7-9 second year students, and transitional students on an orthopedic, neurology, and med-surgical unit.

February 2003 – July 2004 Henry Ford Hospital, Detroit, MI

Registered Nurse

- Worked in a 40 bed Trauma/Surgical Intensive Care Unit caring for multiple trauma and surgical patients. Surgeries included liver and kidney transplants, GI surgeries, orthopedic traumas, vascular, and neurosurgery/head traumas.

January 2002 - June 2002 Eagle Ridge Hospital Coquitlam, B.C.

Registered Nurse

- Attained valuable hospital experience as a surgical nurse
- Mastered importance of collaborative team work ethics by being an active member of the

health care team.

- Assisted in the Emergency Department for the months of May and June.

September 2001 - November 2001 Simon Fraser Health Region, B.C.
Registered Nurse

- Participated in setting up walk-in Flu Vaccine clinics in various locations such as public malls and pavilions.

EDUCATION

September 2015 - current University of California, Irvine

- PhD Candidate at the School of Nursing

March 2013 Lake Arrowhead Regional Medical Center

- Trauma Care After Resuscitation (TCAR) course

May 2011 Lake Arrowhead Regional Medical Center

- Fundamentals of Critical Care Course - Society of Critical Care Medicine

March 29, 2012 HillRom Training Center, Irvine, CA

- Progressive Upright Mobility (PUM) in the ICU Class

September 2005 – January 2010 Cal. State University, Long Beach

- Master of Science in Nursing
- Specialty in Acute Care Clinical Nurse Specialist

February 17, 2003 – March 25, 2003 Henry Ford Hospital, MI

- Completed a Critical Care Course

January 2001 - December 2001 University of British Columbia

- Bachelor of Science in Nursing
- Graduated with Honors; Graduating GPA 3.86
- Completed courses in Pain Management, Palliative care, Nurses and families, Nursing Research, Labor and Delivery, and World Health and Nutrition.

January 1997 - December 2000 Douglas College, B.C.

- Diploma in General Nursing

- Graduating GPA 3.90
- Achieved the Dean's List for the 1998 school year.
- Completed preceptorship/transitional experience in the Emergency Department Overflow at Royal Columbian Hospital, New Westminster, B.C.
- Clinical experiences range in a variety of settings such as maternity, pediatrics, geriatrics, medical/surgical, ambulatory care, community, and mental health.

CERTIFICATIONS

- CCNS
- CCRN

AWARDS

- Awarded the Mary Fewster Scholarship for Excellence in Nursing.
- Awarded Graduate Dean's List Award

PROFESSIONAL MEMBERSHIPS

- Member of the Sigma Theta Tau International Honor Society of Nursing - XI ETA Chapter.
- Member of American Association of Critical Care Nurses
- Member of the Society of Trauma Nurses
- Member of the Trauma Managers Association of California

- Cedars-Sinai Annual Trauma Nursing Conference September 14th, 2018 – Guest Speaker
  - Importance of Early Mobility in the Trauma Patient

- Greater Long Beach and Orange County Chapter of AACN Dinner Symposium March 7th, 2018 - Guest Speaker
  - Early Progressive mobility

- Trauma Managers Association of California July 2017 – Guest Speaker
  - Importance of Early Progressive Mobility in the Trauma Patient

- 9th Annual Critical Care Symposium at Long Beach Memorial Medical Center April 10th, 2017 – Guest Speaker
  - Early Progressive Mobility: Important Considerations that Affect Patient Outcomes

- Abstract Presentation with Dr. Miriam Bender at the Medical Knowledge in a Social World Conference at University of California, Irvine March 2016
  - Objective vs. Subjective Knowledge Debates Within the Evidence Based Healthcare Framework

- Sunrise Session speaker at AACN NTI National Conference May 2015
  - Practical Ways to Implement Early Mobility: Lessons from the Front

- LAC-USC Trauma Update November 14th, 2014
  - Progressive Mobility in Critical Care: Evidence Based Practice Strategies

- Casa Colina Hospital and Centers for HealthCare Course November 8th, 2014
  - Progressive Mobility in Acute Care Patients

- Hoag Hospital Acute Care Conference August 22nd, 2014 - Guest Speaker
  - Progressive Mobility in Acute Care Patients

- Greater Long Beach and Orange County Chapter of AACN Dinner Symposium May 7th, 2014 - Guest Speaker
  - Progressive mobility in sick patients: Is it possible?

- San Fernando Valley Chapter of AACN, 40th Annual Spring Symposium - Guest Speaker February 2014

- Advancing Early Mobility in Critical Care: Evidence Based Strategies for Successful Implementation

EXPERT PANEL REVIEWS

- Basic Knowledge Assessment Tool for Critical Care- version 9 © Published 2015

ABSTRACT

The Prevalence and characteristics of patients with marijuana exposure at the time of injury in moderate or severe traumatic brain injury: A retrospective observational cross-sectional study

By

Dina Elias

Doctor of Philosophy in Nursing Science

University of California, Irvine, 2021

Professor Miriam Bender, Chair

Traumatic brain injury (TBI) is a significant public health concern as it is a leading cause of mortality, morbidity and disability in the United States. According to the World Health Organization, TBI is expected to become the third leading cause of death and disability in the world by 2020. In the United States TBI contributes to a third of all injury-related deaths. The leading causes of injuries resulting in TBI prevalence are traffic related, such as motor vehicle crashes, or non-traffic related, such as falls. Notably, up to 51% of all TBI patients have substance use exposure at the time of injury. Substance use includes alcohol and drugs such as marijuana. Current existing research suggest that in general, substance-exposed patients may have worse TBI outcomes, including greater rates of mortality and severity of injury. Research has also shown that substance use exposed TBI patients suffer worse functional outcomes, which can result in socioeconomic burden to patients and the nation at large. This healthcare burden has been calculated to be approximately $76.5 billion in 2010 alone. There is a substantial body of research elucidating the role alcohol plays in injuries that lead to TBI prevalence and outcomes. Specifically, alcohol use results in impairments such as diminished motor control, blurred vision, and poor decision making, which has been shown to increase the risk of traffic related injury.

This research has been used to create public health policies and prevention programs that have made a significant health impact, such as reducing the number of alcohol-impaired drivers.

Other substances have not been as well studied. For example, marijuana is a drug that despite being federally and legally regulated, remains the most widely used drug in the U.S. Marijuana use has been shown to result in similar cognitive impairments as alcohol use, such as lack of coordination, inability to pay attention, and decision-making abilities, suggesting marijuana users are similarly at increased risk for TBI. There is some indirect evidence of this, in that it has been shown that marijuana users in general are about 25% more likely to be involved in a motor vehicle crash and that the older adult marijuana users have a greater risk for falls. However, concrete data linking marijuana exposure at time of injury and TBI prevalence and severity is scarce. Adding to the concern, national surveys on drug use and health have documented an increase in individual daily marijuana use over the last 5 years. As the number of states legalizing marijuana for both medical and recreational use increases, it is imperative to resolve the ambiguity within the research available regarding the relationships between marijuana exposure at time of injury, mechanism of injury, and TBI prevalence and severity.

This study found that the presence of THC was significantly associated with lower GCS scores and a potentially more severe TBI, but this relationship was significant without controlling for other predicting variables. Furthermore, a significant relationship was found between GCS scores, age, and blood alcohol levels at the time of presentation in the ED. Older participants were found to have higher GCS scores, indicating a less serious brain injury. Study participants who had higher blood alcohol levels were found to have lower GCS scores, indicating a more serious brain injury. Age and higher blood alcohol levels were found to be associated, with higher blood alcohol levels noted in younger patients.

A linear regression showed different results when examining the relationship between the presence of THC and GCS scores, hence TBI severity. When controlling for all other variables, the presence of THC was not found to be an independent predictor of TBI severity. Alternatively, being male, having elevated blood alcohol levels and having other drugs present on admission were all found to have a significant influence on GCS scores and TBI severity, with GCS scores being lower for all three variables, implying a more serious TBI. Similarly, having a diagnosis of cancer, mental or personality disorder and alcohol use disorder were found to have an influence on GCS scores. Participants with a diagnosis of cancer or mental/personality disorder were found to have lower GCS scores, again, implying a more serious TBI. Conversely, participants with a diagnosis or history of alcohol use disorder had higher GCS scores, indicating a less serious TBI.

While the presence of THC initially did show a hypothesized relationship to GCS score (with lower scores indicating higher TBI severity), the relationship became insignificant when adjusted for all the other covariates variables. Because of the large percentage of missing data, the validity of findings, such as THC prevalence rate in this TBI population, should be cautiously interpreted for all the included hypothesized explanatory variables. Further research with datasets that are larger and more complete are needed to fully understand and examine the relationship between marijuana and TBI severity. This study importantly underscores the need for better data to enable better research regarding the relationship between marijuana and TBI severity.

KEY WORDS: marijuana, substance abuse, traumatic brain injury (TBI), TBI severity

CHAPTER 1: RESEARCH PROBLEM

Introduction

What is TBI. Traumatic brain injury (TBI) is a significant public health concern as it is a leading cause of mortality, morbidity and disability in the United States (Taylor et al., 2003). According to the World Health Organization, TBI is expected to become the third leading cause of death and disability in the world by 2020. In the United States TBI contributes to a third of all injury related deaths (Centers for Disease Control and Prevention [CDC], 2015). A traumatic brain injury, as defined by the Centers for Disease Control and Prevention (CDC), is a disturbance of the brain's normal function that occurs when an individual sustains a blow, jolt, or bump to the head, or sustains a penetrating head injury (CDC, 2015). Traumatic brain injuries can lead to a variety of secondary conditions that could result in cognitive, behavioral, motor, and somatic impairments that cause long-term disability and poor quality of life (Taylor, Kreutzer, Demm, & Meade, 2003).

Causes of TBI. The leading causes of injuries resulting in TBI prevalence are traffic related, such as motor vehicle crashes, or non-traffic related, such as falls. Falls are the leading cause of TBI with almost 81% of emergency department (ED) room visits in adults over the age of 65 attributed to falls (CDC, 2019). Motor vehicle collisions are the leading cause of TBI related deaths, with rates being highest for adults between the ages of 15-24, 25-35 and older adults greater than 75 (CDC, 2019; Faul, Xu, & Coronado, 2010).

Substance use and TBI. Notably, up to 51% of all TBI patients have substance use exposure at the time of injury (Corrigan, 1995; Parry-Jones, Vaughn, & Miles, 2006; Niemeier et al., 2016). Substance use includes alcohol and drugs such as marijuana. Current existing research suggest that in general, substance-exposed patients may have worse TBI outcomes, including greater rates of mortality

and severity of injury. Research has also shown that these patients suffer worse functional outcomes, which can result in socioeconomic burden to patients and the nation at large. This healthcare burden has been calculated to be approximately $76.5 billion in 2010 alone (CDC, 2015).

Substance use and mechanisms of injury. There is a substantial body of research elucidating the influence of alcohol on TBI prevalence and outcomes (Niemeier, 2016). Alcohol use results in impairments such as diminished motor control, blurred vision, and poor decision making, which in turn has been shown to increase the risk for TBI (Sewell, Poling & Sofuoglu, 2010). This research has been used to create public health policies, public education efforts, and prevention programs that have made a significant health impact, such as reducing the number of alcohol-impaired drivers (National Academies of Sciences, Engineering, and Medicine, 2018). While it is known that there is significant alcohol use related to TBI, little is known about the influence of marijuana on the prevalence, severity and outcomes related to TBI (Andelic, 2010).

Marijuana use and mechanisms of injury. Marijuana is an drug that despite being federally and legally regulated, remains the most widely used drug in the U.S. (Wilkinson, Yarnell, Radharkrishnan, Ball, & D'Souza, 2016). Marijuana use has been shown to result in similar cognitive impairments as alcohol use, such as lack of coordination, alterations in reaction time, inability to pay attention, and decision-making abilities, suggesting marijuana users are similarly at increased risk for TBI (Volkow et al., 2016; Volkow, Baler, Compton & Weiss, 2014). There is some indirect evidence of this, in that it has been shown that marijuana users in general are about 25% more likely to be involved in a motor vehicle collision (MVC) and that the older adult marijuana users have a greater risk for falls (CDC, 2019). Both short and long-term marijuana exposure has been shown to impair driving ability; marijuana is the drug most often reported in association with impaired motor vehicle collisions, including fatal ones (Volkow et al., 2014). It has also been shown that the overall risk of being involved

in a motor vehicle collision increases by a factor of 2 soon after an individual has used marijuana (Hartman & Huestis, 2013). Motor vehicle collisions make up almost two thirds of U.S. trauma center admissions and are the leading cause of TBI related deaths (Hartman & Huestis, 2013; Faul, Xu & Coronado, 2010). Approximately 60% of MVC patients tested positive for drugs and alcohol (Hartman & Huestis, 2013). Despite the increase in marijuana use and exposure, concrete data linking marijuana exposure at time of injury and TBI prevalence and severity is scarce (Hartman & Huestis, 2013). Adding to the concern, national surveys on drug use and health have documented an increase in individual daily marijuana use over the last 5 years.

Study Objectives

In summary, there is no body of research documenting the relationship between marijuana exposure and TBI prevalence and severity. As the number of states legalizing marijuana for both medical and recreational use increases, it is imperative to resolve the ambiguity within the research available regarding the influence of marijuana exposure on TBI. This study will fill important gaps in knowledge about this emerging public health concern by documenting the prevalence of marijuana exposure in a national sample of TBI patients, and determine the relationship between marijuana exposure, mechanism of injury, and TBI severity. Study aims are to: 1) assess the prevalence of marijuana exposure in patients with moderate or severe TBI at time of injury; 2) examine correlates associated with marijuana exposure at the time of injury; and 3) examine the relationship between marijuana exposure, mechanism of injury and TBI severity. Results will provide the first quantifiable national-level evidence of the impact of marijuana exposure on TBI. Results will also serve as the basis for research that can inform policy and public safety standards and metrics regarding marijuana exposure and its effect on TBI.

CHAPTER 2: LITERATURE REVIEW

Traumatic Brain Injury, as defined by the Center for Disease Control and Prevention (CDC), is a disturbance of the brain's normal function that occurs when an individual sustains a blow, jolt or bump to the head, or sustains a penetrating head injury. (Centers for Disease Control and Prevention, 2015) Traumatic brain injury severity is classified as mild, moderate or severe, based on Glasgow Coma Scale (GCS) scores, duration of altered mental state or loss of consciousness, and post-trauma amnesia. (Centers for Disease Control and Prevention, 2015). Falls are the leading cause of TBI prevalence, and the leading cause ED room visits in adults over the age of 65 (CDC, 2019). Moreover, MVCs are the leading cause of TBI related deaths, with rates being highest for adults between the ages of 15-24, 25-35 and older adults greater than 75 (CDC, 2019; Faul, Xu, & Coronado, 2010).

Motor vehicle collisions make up almost two thirds of U.S. trauma center admissions and are the leading cause of TBI related deaths (Hartman & Huestis, 2013; Faul, Xu & Coronado, 2010). Notably, approximately 60% of MVC patients tested positive for drugs and alcohol (Hartman & Huestis, 2013). Available literature denotes that a significant number of individuals sustaining a TBI were found to have used substances, such as alcohol or marijuna, with approximately 36 to 51% of individuals showing some form of substance use when admitted to an emergency department. (Corrigan et al., 2012; Niemeier et al., 2016; Parry-Jones, Vaughan, & Miles Cox, 2006).

Despite being federally and legally regulated, marijuana remains the most widely used drug in the world, as well as in the U.S. (Asbridge, Hayden, & Cartwright, 2012; Wilkinson, Yarnell, Radhakrishnan, Ball, & D'Souza, 2016) Marijuana, a commonly used drug, is a complex agent that contains a combination of more than 100 chemicals, including cannabinoids

and flavonoids. (Wilkinson et al., 2016) The primary component of marijuana is delta-9-tetrahydrocannabinol (THC), and it is THC that is thought to cause the psychoactive effects associated with marijuana use. (Wilkinson et al., 2016) Approximately 26 million individuals reported using marijuana in the month prior to the 2017 National Survey on Drug Use and Health (NSDUH). (Substance Abuse and Mental Health Services Administration, 2018) Furthermore, the number of daily marijuana users increased from 5.1 million individuals in 2005-2007, to 8.1 million individuals in 2013 (Substance Abuse and Mental Health Services Administration, 2014).

Despite being identified as the most commonly used drug in the U.S., little is known about marijuana exposure and TBI prevalence and severity, particularly at the time of injury (Wilkinson et al., 2016). Virtually nothing is known about the relationship between marijuana exposure and TBI. Therefore, the purpose of this systematic literature review was to determine 1) the prevalence of marijuana exposure in moderate to severe TBI, and 2) the relationship between marijuana exposure and TBI severity.

Search Strategy

A search strategy was implemented by searching the PUBMED electronic bibliographic database between January 17-19 in 2019. No restrictions were applied on publication status and publication date. This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The search strategy included the terms traumatic brain injury, severity, substance, substance abuse, marijuana, THC, cannabis, and drug use. Only publications in English were sought. Reference lists of review papers were searched to ensure all relevant literature was included. An example of the search strategy for this review is shown in Figure 1.

Inclusion Criteria

To be included in this systematic review, studies must have been peer-reviewed, published in English, involve human subjects only, and must have investigated the use of marijuana in adult patients (>16 years of age) reported to have sustained a moderate to severe TBI. We did not consider participants below the age of 16 because pediatric trauma patients present differently than do adults, and are treated with different intervention protocols than in adults. A preliminary search identified the fact that articles subsumed marijuana exposure under the broader umbrella term of substance use/abuse. Therefore, substance and substance abuse terms were included to ensure a wide sensitivity to studies involving drugs such as marijuana.

Exclusion criteria

Patients with a diagnosis of mild TBI were excluded because up to 40% of mild TBI patients do not seek medical attention, and therefore, findings would not be representative (Demakis & Rimland, 2010). Similarly, the following studies were excluded from this review: studies that did not assess for marijuana exposure at time of injury, marijuana post-TBI, cellular based studies, clinical review papers, editorials, case reports, pediatric studies and studies using nonhuman subjects.

Selection Process

Study selection was conducted in a two-stage process. First, studies were screened by titles and abstracts for potential inclusion. Next, studies identified as relevant for potential inclusion underwent a full-text evaluation. Studies that included any information about marijuana exposure at the time of injury were included, including studies where marijuana was bundled with other substances as either a variable or via analysis, because it was assumed there would still be relevant information embedded within the study. The studies were reviewed a second time to ensure all inclusion criteria were met and included if they did.

Data Collection Process

Data was extracted from studies that met selection criteria. Data from the studies were used to achieve the primary aims of this systematic review: to examine marijuana exposure and use in TBI prevalence, severity and outcomes. The following data were abstracted to summarize specific study features and address the review's aims: 1) study characteristics, including authors names, publication year, country, design, sample size, and methods utilized, 2) participant characteristics such as mean age and type of TBI, 3) information about whether other substances besides marijuana, such as alcohol, methamphetamines, cocaine, opiates, benzodiazepines, narcotics, stimulants, speed, hallucinogens and heroin were documented and/or analyzed 4) results, including the prevalence of marijuana, TBI outcomes, and if a relationship between marijuana and TBI was present.

Data Management

Search results, including abstracts and full-text articles, were exported to an Excel file for data management. The decision for inclusion or exclusion in the review process was recorded in the Excel file, as well as a rationale for exclusion of studies. Reference management was done through the Papers©, a reference management software used to manage bibliographies and references. A reference library of PDF documents was maintained through the software and allows a variety of features such as collecting, curating, merging of studies as well as the insertion of citations in-text.

Risk of Bias and Methodological Quality Appraisal in Individual Studies

Level of evidence and risk of bias were assessed for each of the included studies. The Levels of Evidence were assessed using the National Heart, Lung and Blood Institute (NHLBI) categories. The NHLBI Levels of Evidence framework rates evidence on four major levels,

placing the highest rating on evidence that is acquired from Randomized Controlled Trials (RCTs) with an extensive body of data; RCTs are assigned a level "A" according to the NHLBI. Level B studies are RCTs with a limited body of data, usually involving a smaller sample size, include a subgroup analysis of RCTs, and may include study results that are inconsistent. Level C studies are those that employ a non-randomized study design, such as observational studies. Finally, Level D studies include studies that utilized mechanism-based reasoning that involve anecdotal findings based on expert opinion.

Risk of bias of included articles was assessed using the National Heart, Lung and Blood Institute quality assessment tool for observational cohort and cross-sectional studies. (National Institutes of Health, 2014) The NHLBI offers six various study quality assessment tools, three of which apply to observational cohort studies, cross-sectional studies, and case series studies. The quality assessment of observational cohort and cross-sectional studies tool was utilized. The NHLBI quality assessment tool is comprised of 14 criteria/questions that address study objectives, study population, sample size, exposures and outcome measures, and key potential confounding variables. An example of NHLBI quality assessment tool for observational cohort and cross-sectional studies is presented in Table 2.

Potential sources of bias were rated as either "yes", "no", "cannot determine", "not applicable", or "not reported". Each study was given an overall bias rating of good, fair, or poor. Table 2 delineates responses to each of the 14 questions in the NHLBI quality assessment tool, while Table 3 addresses the types of biases encountered, the presence or lack thereof of confounding variables, and other information that aid in the assessment of biases.

Data Analysis and Synthesis

Results from the included studies were reviewed for the outcome of interest and were reported under seven themes: (i) presence of marijuana exposure; (ii) time frame in which marijuana exposure was measured; (iii) method used to measure marijuana exposure; (iv) information on other substances if they were bundled with marijuana exposure; and (v) the presence of a specific link between marijuana exposure and TBI severity. Due to the range and diversity of study results and designs, a meta-analysis was not possible. Additionally, given the differences in the conceptualization and definition of marijuana exposure across the studies included, and the heterogeneity in methods, sample data, collection and findings, a narrative interpretation and descriptive analysis of the findings was necessary.

RESULTS

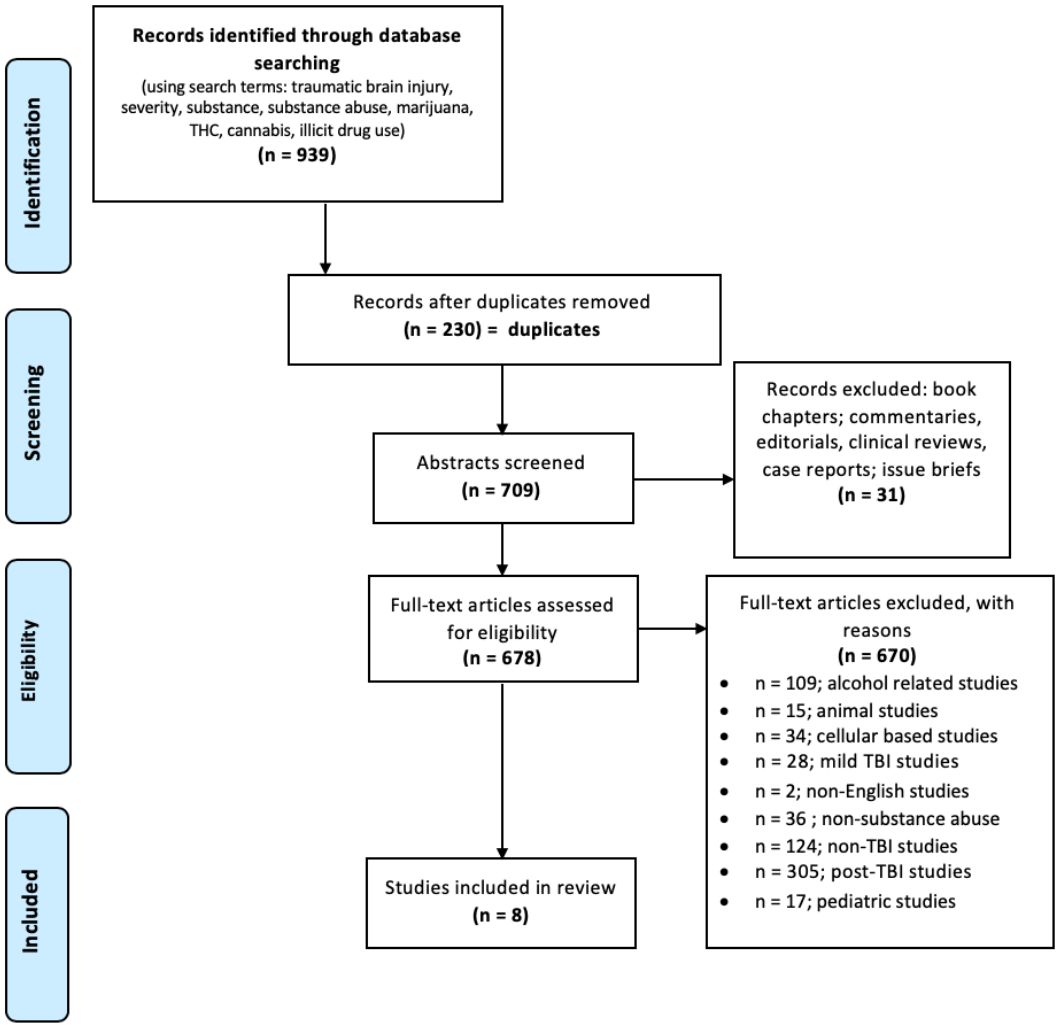
Selected Studies

The literature search yielded 939 studies (Figure 1). After duplicates were removed, 710 records remained; studies were then eliminated according to the inclusion and exclusion criteria as mentioned above. A total of 31 studies were excluded based on the following sub-categories: nine studies were excluded because they were case reports, 1 because it was a book chapter, 16 because they were clinical reviews, 2 because they were commentaries, 1 because it was an editorial and 2 because they were issue briefs. This was followed by the exclusion of 305 studies because they investigated substance abuse because of TBI, hence post-TBI. Then, 124 studies were excluded because they investigated conditions other than TBI, while another 28 studies were excluded because they only investigated participants who had sustained a mild TBI. Thirty-four studies were excluded based on investigating cellular morphology and changes in TBI patients; a subject that surpasses the purpose of this study. One hundred and nine studies were excluded because they did not examine marijuana; these studies investigated alcohol as the

primary, and at times, the only substance utilized by participants. A further 15 studies were excluded because the studies involved non-human participants. Thirty-six studies were excluded because they did not investigate the use of any substances in their TBI participants. Finally, 2 studies were eliminated because they were non-English publications, and 17 studies were further excluded on the grounds of including participants aged 16 years or younger. A total of 8 studies met eligibility requirements for final inclusion. See Figure 1 for an illustration of the exclusion process.

Figure 1

Search Algorithm and Included Studies



Study Design and Quality Appraisal

Study quality and risk of bias for each of the included studies, according to the NHLBI quality assessment tool for observational cohort and cross-sectional studies, is presented in Table 1. All eight studies employed an observational cohort study design and were assigned a "C" Level of Evidence. One of the studies (Andelic et al., 2010) included a prospective cohort study design while the remaining seven studies included a retrospective study designs. The prospective study (Andelic et al., 2010) was assessed as a good study as the investigators had control over

the quality, accuracy and completeness of collected data. In the remaining seven studies, a retrospective approach was used where investigators had to rely on pre-existing data that could not be confirmed nor deemed reliable. This creates a susceptibility to recall bias and attrition bias. Though not highly esteemed as randomized controlled studies, observational cohort studies can be efficient in answering specific type of research questions. However, special attention must be given to the presence of potentially confounding factors. Only four of the eight studies included addressed confounding factors; rendering the remaining four studies a "fair" quality rating.

Table 1

Study Quality Assessment using the National Heart, Lung and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-sectional Studies

		NHLBI question*														
First author	LOE	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Rating
Andelic	C	Y	Y	Y	Y	NA	Y	Y	Y	Y	N	Y	Y	NA	Y	Good
Barker	C	Y	Y	Y	Y	NA	Y	Y	N	Y	N	Y	Y	NA	Y	Good
Bombardier	C	Y	Y	Y	Y	NA	Y	Y	N	Y	N	N	Y	NA	N	Fair
Kolakowsky-Hayner	C	Y	Y	Y	Y	NA	Y	Y	N	Y	N	N	Y	NA	N	Fair
Kreutzer	C	Y	Y	Y	Y	NA	Y	Y	N	Y	Y	N	Y	NA	N	Fair
Nguyen	C	Y	Y	Y	Y	NA	Y	Y	N	Y	N	Y	Y	NA	Y	Good
O'Phelan	C	Y	Y	Y	Y	NA	Y	Y	Y	Y	N	Y	Y	NA	Y	Good
Pakula	C	Y	Y	Y	Y	NA	Y	Y	Y	Y	N	Y	Y	NA	N	Fair

* 1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Participants in each of the eight studies were selected based on the presence of a TBI, with some studies including TBI severity in their definition of TBI. Based on the study designs utilized by included studies, selection bias regarding sampling was anticipated as participants are not randomized, rather they are selected based on the outcome and exposure of interest; in such study designs, convenience sampling is most often utilized. Due to the nature of the studies included in this review, allocation concealment and blinding of outcomes assessors is not feasible. Because the exposure of substance abuse has not been allocated randomly, a causal effect may not be possible as other variables may be found to influence the outcomes studied, rendering all eight studies at a major disadvantage with potential bias in outcomes.

Study methods employed by each of the eight included studies varied with some studies utilizing medical chart reviews, while others utilized validated surveys and questionnaires to gather their data. The studies by Andelic et al., (Andelic et al., 2010) Barker et al., (L. H. Barker et al., 1999) and Bombardier et al. (Bombardier, Rimmele, & Zintel, 2002) all utilized the participants' medical charts for retrospective review for presence of substances. The studies by Andelic et al., (Andelic et al., 2010) Nguyen et al., (Nguyen et al., 2014) and O'Phelan et al. (O'Phelan et al., 2008) used trauma registry databases to collect data on TBI patients and the presence of substance abuse. Pakula et al. (Pakula, Shaker, Martin, & Skinner, 2013) collected data on the presence of substance abuse in post-mortem patients with traumatic cranial injuries by evaluating autopsy reports. Finally, the studies by Bombardier et al., (Bombardier et al., 2002) Kolakowsky-Hayner et al., (Kolakowsky-Hayner et al., 2002) and Kreutzer, Witol and Marwitz (Kreutzer, Witol, & Marwitz, 1996) utilized questionnaires to interview participants. The

variance in study methods, ranging from retrospective review of charts to the use of self-report methodology subjects the included studies to recall bias and unreliable data.

A factor negatively contributing to the quality of the included studies is the variance in defining a TBI. Three of the studies (Bombardier et al., 2002; Kolakowsky-Hayner et al., 2002; Kreutzer et al., 1996) did not provide a definition for what constitutes a TBI, nor did they describe the severity of TBI. The study by Andelic et al. (Andelic et al., 2010) defined TBI using the TBI Modified Marshall Classification. The study by Barker et al. (L. H. Barker et al., 1999) defined TBI using the TBI Model Systems Data Base definition. Nguyen et al. (Nguyen et al., 2014)used the International Classification of Diseases-Ninth Revision codes (ICD-9-CM) and the Abbreviated Injury Severity (AIS) codes to define TBI. These codes are widely used in trauma data registries for entering and recording the injury type and severity, for performance improvement and billing purposes. However, reliability can be an issue as coding may be subjective. The information is extracted from the chart by registrars who read and enter notes written by physicians. Often, coding depends on physician documentation, attention by trauma registrars to the various sources of documentation and communicating with physicians when necessary. If not subject to continuous data validation, a data gap may ensue. The study by Pakula et al. (Pakula et al., 2013) defined a central nervous system injury by the presence of any of the following written diagnosis as found in the autopsy reports: 1) TBI, 2) skull base fracture, 3) spinal cord injury, and 4) cervical spine injury. Only one study, the study by O'Phelan utilized a Glasgow Coma Score to define a severe TBI.

Risk of bias in terms of selection and information was determined for each study. The majority of the articles were subject to selection bias in terms of their participant population and methods of data collection: See table 2 for specifics.

Table 2

Types of Biases

First Author, Year	Risk and Type of Bias?	Potential Biases	Overall Quality
Andelic, 2010	Selection bias Informational bias	Not all TBI patients would be captured as not all patients may present to a trauma hospital. Study utilized diagnosis coding which primarily depends on data analyst's extraction of data from the medical charts and inputting data into the hospital registry. Also, potential informational bias in providers documenting the incorrect diagnosis code.	Good
Barker, 1999	Selection bias Informational bias	Not all TBI patients would be captured as not all patients may present to a trauma hospital. Small sample size. Study utilized diagnosis coding which primarily depends on data analyst's extraction of data from the medical charts and inputting data into the hospital registry. Also, potential informational bias in providers documenting the incorrect diagnosis code.	Good
Bombardier, 2002	Selection bias Recall bias	Did not specify what types of TBI severity the study was including; unspecified whether mild, moderate or severe. A survey questionnaire was administered creating recall bias due to self-report of history of substance abuse.	Fair
Kolakowsky-Hayner, 1999	Selection bias Recall bias	Did not specify what types of TBI severity the study was including; unspecified whether mild, moderate or severe. Small sample size. A survey (GHH questionnaire) was administered creating recall bias due to self-report of history of substance abuse.	Fair
Kreutzer, 1996	Selection bias Recall bias	Did not specify what types of TBI severity the study was including; unspecified whether mild, moderate or severe. Small sample size. A survey questionnaire (GHH Questionnaire) was administered creating recall bias due to self-report of history of substance abuse.	Fair
Nguyen, 2014	Selection bias Informational bias	Study only utilized patients who presented at one facility; population may not be reflective demographically nor characteristically with the general population. Study utilized diagnosis coding which primarily depends on data analyst's extraction of data from the medical charts and inputting data into the hospital registry. Also, potential informational bias in providers documenting the incorrect diagnosis code.	Fair
O'Phelan, 2008	Selection bias Informational bias	Not all TBI patients would be captured as not all patients may present to a trauma hospital. Study utilized diagnosis coding which primarily depends on data analyst's extraction of data from the medical charts and inputting data into the hospital registry. Also, potential informational bias in providers documenting the incorrect diagnosis code.	Good
Pakula, 2013	Selection bias Informational bias	Study selected all patients with central nervous system injuries, which is not quite specific nor selective to the TBI population. Many potential confounders exist such as mechanism of injury as well as patient characteristics. A Review of autopsy reports subjects the study to informational bias because not all coroner offices perform full autopsy reports on cases, rather, they refer to the provider's death certificate documentation if the injury is not related to a criminal case or due to a special request for a full autopsy by family or hospital.	Fair

Study Participants and Characteristics

Of the 8 included studies, 7 were conducted in the U.S., and 1 in Norway. Participants' age ranged from 18-49 years. One study had an all-male sample, while the remaining 7 had a larger male than female participant percentage ranging from 74% (n=357) to 92% (n=48). All the studies included participants who had sustained a moderate or severe TBI. Three studies included participants who had been admitted to a trauma hospital and were followed as patients in an inpatient rehabilitation unit, while 3 studies similarly included participants who had been admitted to a trauma center but were not followed throughout their rehabilitation phase. One study included participants in an outpatient rehabilitation setting, while one study included post-mortem participants. See Table 3 for details.

Table 3

Included Article Characteristics

Author, Year	Location	Design	Sample Size	Mean Age (years)	Methods	Inclusion Criteria	Main Outcome Measures
Andelic, 2010	Norway	Prospective Observational Cohort	111	31.7; 32.6	Prospective study of acute TBI patients at a trauma referral center over a two year period using systematic medical chart review and data review from trauma registry.	ICD 10 S06.0-S06.9 within 24 hours; moderate to severe TBI Known status of substance abuse at time of injury Brain CT performed within 24 hours post-injury	Substance abuse at time of injury Substance abuse pre-injury Substance abuse effect on TBI severity
Barker, 1999	United States	Retrospective Observational Cohort	44	23.74	Retrospective medical chart review to determine presence of substance abuse in TBI patient group and in TBI patients with no substance abuse.	Hospitalized and admitted with a TBI diagnosis Scanned at least 6 weeks post injury	MRI findings in older adolescents with substance abuse
Bombardier, 2002	United States	Retrospective Observational Cohort	142	37.4	A survey was administered by a trained interviewer. Retrospective review of medical charts relevant medical diagnostic and clinical information	No cognitive impairment English speaking Greater than 18 years of age No history of severe psychiatric disorder First/initial rehabilitation admission Discharge disposition not to include homeless shelter or prison	Substance abuse pre-injury
Kolakowsky-Hayner, 1999	United States	Retrospective Observational Cohort	52	38.27	GHH Questionnaire administered to participants and/or family members during rehabilitation stay.	Spinal cord or TBI patient in rehabilitation facility	Substance abuse pre-injury in SCI patients Substance abuse pre-injury in TBI patients Comparison between SCI and TBI groups
Kreutzer, 1996	United States	Retrospective Observational Cohort	87	16-20	GHH Questionnaire mailed to participants prior to scheduled physical and/or neuropsychological examination	Less than 21 years of age	Substance abuse pre-injury
Nguyen, 2014	United States	Retrospective Observational Cohort	446	49.4	Retrospective review of hospital trauma registry data	Diagnosis of TBI Urine toxicology screen performed	Relationship between positive THC screen and TBI outcomes
O'Phelan, 2008	United States	Retrospective Observational Cohort	483	41.8	Retrospective review of medical records in trauma registry	Admission to medical center from 2001-2006 GCS < 9 Mechanism of injury consistent with blunt trauma Diagnostic codes indicating head injury	Substance abuse at time of injury Effect of substance abuse on in-hospital mortality in TBI patients
Pakula, 2013	United States	Retrospective Observational Cohort	790	18-49	Evaluation of autopsy reports	Central nervous system injuries	Behavior patterns in traffic related fatalities associated with CNS injuries

Traumatic Brain Injury Characteristics

The included studies varied in their definition of TBI. One study used the Modified Marshall Classification of TBI which is a Computed Tomography (CT) scan derived metric used to grade acute TBI on the basis of CT findings. (Mahadewa, Golden, Saputra, & Ryalino, 2018)Another study defined TBI using the TBI Model Systems National Database (TBIMS-NDB) definition. The TBIMS-NDB has been funded by the National Institute on Disability and Rehabilitation Research in the U.S. Department of Education to study the course of recovery and outcomes following a TBI. (Corrigan et al., 2012) They describe the TBIMS-NDB TBI as: Damage to brain tissue caused by an external mechanical force as evidence by medically documented loss of consciousness or post-traumatic amnesia (PTA), or by objective neurological findings on physical or mental examination that can be reasonably attributed to TBI. (p. 2) Three of the eight studies did not specify how TBI was defined. One study used the following International Classification of Disease, 9th Revision (ICD-9-CM) codes to define TBI: 800.1-800.39 (closed fracture of vault of skull with cerebral laceration and contusion); 800.6-800.89 (fracture of vault of skull); 801.1-801.39 (closed fracture of base of skull with cerebral laceration and contusion); 801.6-801.89 (fracture of base of skull); 803.6-803.89 (other and unqualified skull fractures); 804.6-804.79 (fractures with intracranial bleed); 851 (cerebral laceration and contusion, all); 852 (subarachnoid hemorrhage, subdural hemorrhage, extradural hematoma after injury, all) and 853 (other and unspecified intracerebral hemorrhage). Another study used the International Classification of Disease, 10th Revision (ICD-10-CM) codes to define TBI: S02.0xx (fractures of vault of skull); S02.1 (fractures of base of skull); S06.1 (traumatic cerebral edema); S06.2 (diffuse traumatic brain injury); S06.3 (focal traumatic brain injury); S06.31(contusion and laceration of right cerebrum); S06.32 (contusion and laceration of left cerebrum); S06.33

(contusion and laceration of cerebrum unspecified) and S09.x (unspecified intracranial injury). Finally, the last of the eight studies used autopsy reports to evaluate individuals with severe central nervous system (CNS) injuries. For purposes of that study, severe CNS injuries were defined as "any traumatic brain injury, skull base fracture, spinal cord injury, or cervical spine injury." (Pakula et al., 2013)

Marijuana Exposure Characteristics

Key summary findings can be found in Table 4. Six studies identified marijuana exposure at the time of injury, (Andelic et al., 2010; L. H. Barker et al., 1999; Bombardier et al., 2002; Nguyen et al., 2014; O'Phelan et al., 2008, Kreutzer et al., 1996) while two studies identified participants' marijuana exposure as far back as one year before sustaining the traumatic injury. (Kolakowsky-Hayner et al., 2002; Kreutzer et al., 1996) All the studies investigated a range of potential substance use beyond marijuana exposure, including both drugs and alcohol, with the exception of one study by Nguyen et al. (Nguyen et al., 2014) that focused solely on marijuana use. The specific drugs identified included amphetamines, cocaine, hallucinogens, heroin, opiates, speed, benzodiazepines, marijuana. Incidentally, marijuana was the most frequently drug reported used by participants.

Table 4

Summary of Key Study Findings and Outcomes associated with Marijuana Use

Author, Year	Moderate and/or Severe TBI	THC measured?	THC measured at time of injury?	Other time THC measured	How was THC measured?	Other drugs measured	Most frequent or favored drug measured	Alcohol measured?	A specific link between THC and TBI identified?	Overall Findings
Andelic, 2010	Yes	Yes	Yes	Pre-injury	Urine	NS	Marijuana	Yes	No	At time of injury, frequency of SA in less in severe TBI. Pre-injury SA is higher in severe TBI. SA at time of injury decreased probability of a more severe TBI.
Barker, 1999	Yes	Yes	Yes	Pre-injury	Clinical documentation Urine toxicology	Amphetamines, cocaine	NS	Yes	No	SA in combination with TBI results in greater atrophic changes.
Bombardier, 2002	NS	Yes	Yes	Pre-injury	Urine toxicology	Amphetamines, cocaine, hallucinogens and heroin	Marijuana	Yes	No	Alcohol and drug use common before TBI.
Kolakowsky-Hayner, 1999	NS	Yes	No	Past year use	Self-report	Cocaine, opiates, heroin, speed, stimulants	Marijuana	Yes	No	Rate of pre-injury drinking for TBI and spinal cord injury high.
Kreutzer, 1996, 1996	NS	Yes	Yes	Past year use	Self-report	Cocaine	Marijuana	Yes	No	Individuals with history of pre-injury heavy drinking are at greatest risk for long-term alcohol abuse.
Nguyen, 2014	Yes	Yes	Yes	At time of injury	Urine toxicology	N/A	N/A	No	Yes	Positive THC screen is associated with a decreased mortality in TBI.
O'Phelan, 2008	Yes	Yes	Yes	Pre-injury At time of injury	Urine toxicology	Amphetamines, benzodiazepine, narcotics, cocaine	NS	Yes	No	Alcohol and methampheta mine use are associated with decreased mortality.
Pakula, 2013	Yes	Yes	No	Post-mortem	Urine toxicology	NS	NS	Yes	No	Substance abuse and distracted driving are prominent patterns of high-risk behavior in MVCs

*SA = substance abuse
*NS = non-specified
*N/A = non-applicable

The procedures by which the presence of marijuana exposure was detected varied across the selected studies. In some of the studies, (Andelic et al., 2010; P. M. Barker, Reid, & Schall, 2016; Bombardier et al., 2002; O'Phelan et al., 2008, Pakula et al., 2013) marijuana was detected via a positive urine drug screen or via blood alcohol levels. In addition to utilizing toxicology screening results to identify the presence of marijuana, the studies by Andelic et al., (Andelic et al., 2010) Kolakowsky-Hayner et al., (Kolakowsky-Hayner et al., 2002) and Kreutzer et al. (Kreutzer et al., 1996) also utilized the General Health and History Questionnaire (GHHQ) to gather self-reported patient incidence or marijuana exposure. As described earlier, the GHHQ questionnaire aims at assessing the psychosocial, neurobehavioral and vocational status of patients with traumatic injuries. (Kolakowsky-Hayner et al., 2002)

Marijuana and Study Characteristics

Although all eight studies investigated marijuana exposure in TBI patients, only one study (Nguyen et al., 2014) specifically investigated the use of marijuana alone on outcomes in TBI. All other remaining studies investigated the presence of all possible substances and/or drugs, meaning investigators were not specifically examining marijuana exposure by itself. In Nguyen et al. (Nguyen et al., 2014) all patients who had sustained a TBI and had a urine toxicology screen were included. The actual noted presence of marijuana was obtained from the urine toxicology screen and not through any other modes of measurement. The authors classified study patients according to marijuana screen results which they defined as greater than 50 ng/ml.

Though marijuana was noted to have been detected across all eight studies, the actual numerical or absolute value measured was never reported by any of the studies. Additionally, it is important to note that excluding the study by Nguyen et al., (Nguyen et al., 2014) the presence

of marijuana was not reported in a quantifiable manner, making any potential statistical inference impossible. Lastly, six of the included studies investigated the presence of marijuana at the time of injury, (Andelic et al., 2010; L. H. Barker et al., 1999; Bombardier et al., 2002; Kreutzer et al., 1996; Nguyen et al., 2014; O'Phelan et al., 2008) while the remaining two studies (Kolakowsky-Hayner et al., 2002; Pakula et al., 2013) measured the presence of marijuana use during the past year and post-mortem respectively. The study by O'Phelan et al. (O'Phelan et al., 2008) did not investigate any other time frame for which marijuana may have been used, rather, the authors only collected data on the presence of drugs at the time of injury.

Marijuana and TBI Outcomes

An important finding from the systematic literature review showed that marijuana was the most favored drug reported. However, only one study of the eight studies included explicitly searched for and found a connection between the presence of a positive toxicology screen for marijuana and mortality outcomes in TBI patients. (Nguyen et al., 2014) Nguyen et al. (Nguyen et al., 2014) three-year retrospective review of trauma registry data found that 18.4 (82 of 446 cases) percent of all cases meeting inclusion criteria had a positive marijuana screen and overall mortality was 9.9 percent (44 of 446 cases). Nguyen et al. (Nguyen et al., 2014) found that mortality in the marijuana positive group (2.4% [2]) was significantly lower when compared to the marijuana negative group (11.5% [42]; $p = 0.012$). Authors adjusted for the following differences between study participants: age, gender, ethnicity, alcohol, abbreviated injury scores, injury severity scores, and mechanism of injury. After adjusting for differences, Nguyen et al. (Nguyen et al., 2014) found that a positive marijuana screen was an independent predictor of survival in TBI patients (Odds ratio [OR], 0.224; 95% confidence interval [CI], 0.051 to 0.991; $p = 0.049$).

The study by Pakula et al. (Pakula et al., 2013) examined patterns of behavior in motor vehicle and motor cycle drivers that are associated with central nervous system related pre-hospital deaths. The authors examined 514 fatalities of which 95% (n=491) were a result of motor vehicle collisions (MVCs). Of the 491 MVC fatalities, there were 358 drivers and 133 passengers. Toxicology screen data revealed that nearly 13% of drivers (n=46) were positive for cannabinoids.

Discussion of the Literature Review

This review sought to determine the use of marijuana and its role in TBI prevalence and outcomes. A key finding from this review is that there are few studies available that examine the specific role of marijuana exposure on TBI severity, leaving many questions unanswered. Furthermore, this review found that there is a significant variation in how substance abuse has been defined, conceptualized, and operationalized in TBI research. Another important finding was that the reviewed studies operationalized substance abuse inconsistently, often combining alcohol and drugs in one category titled 'substance abuse,' making it difficult to ascertain if there was an association between specific drugs, particularly marijuana, and TBI severity and outcomes. The difference in how substance abuse was operationalized in these reviewed studies has important implications for how findings are interpreted as well as provide recommendations for future research.

Although there was no restriction made to the countries in which these studies were conducted, those meeting inclusion criteria were all studies conducted in the US except one from Norway. (Andelic et al., 2010) Therefore, the applicability of findings from that one non-American study is limited. Additionally, it is difficult to draw valid and reliable conclusions when the studies reviewed utilized a wide variety of study objectives, sample size, study methods, and varying definitions for substance abuse classification.

The review showed a great variation existed across the studies in types of data collected and methods used, thus severely minimizing comparability. For example, the disparity in measurement of blood alcohol levels considerably reduce the reliability of data related to pre-injury intoxication. In the reviewed studies, information on alcohol and substance use was obtained from a range of different sources, including self-reports and patient records, as well as a variety of different measures rendering results unreliable across studies.

What Influence does Marijuana Exposure have on TBI Prevalence and Severity?

This review set out to answer a specific question: what influence, if any, does marijuana exposure at time of injury have on TBI severity and outcomes? Only one study about marijuana's effect on TBI outcomes was available. Nguyen et al. (Nguyen et al., 2014) reported that a positive marijuana screen is an independent predictor of survival, suggesting a potential neuroprotective effect of cannabinoids in TBI. The rest of the studies yielded a variety of findings, with the most common finding being that marijuana and other drug use, including alcohol, are common before TBI.

Potential Confounding Variables

To clearly understand what marijuana's influence on TBI is, potential confounding variables must be identified and controlled for. The literature review identified no consensus on relevant confounding variables aside from age and gender. The variability in all other demographic variables highlights the lack of certainty of the full range of relevant demographic variables. Another potentially important confounding variable is mechanism of injury. Historically, the most frequent cause of TBI related deaths in civilians was considered motor vehicle crashes. However, recent data show that falls are actually the leading cause of TBI-related hospitalizations, with the second leading cause is being struck by another object.

(Meaney, Morrison, & Bass, 2014) Importantly, only six of the studies included mechanism of injury as a variable in their analysis of findings.

Five of the eight included studies did not address TBI severity as a variable. (L. H. Barker et al., 1999; Bombardier et al., 2002; Kolakowsky-Hayner et al., 2002; Kreutzer et al., 1996; Pakula et al., 2013) The remaining three studies each operationalized TBI severity utilizing different methods. Andelic et al. (Andelic et al., 2010) used the Marshall classification to classify neurological anatomical abnormalities as seen on CT scans. Nguyen et al. (Nguyen et al., 2014) utilized the Abbreviated Injury Scale (AIS) score for the head and neck region to classify TBI severity. The use of the AIS score is common in general research studies as often times the GCS score is not always recorded for each individual participant. Hence the only study showing a link between marijuana exposure and TBI severity did not use the gold standard of GCS to measure TBI specific severity. Finally, severity as a variable in the TBI population is an important characteristic and is a parameter of interest when answering the research question of whether or not marijuana influences TBI severity; available studies are not able to answer that question mostly because the majority of them did not measure severity in the first place. Severity is important because it provides a level of specificity about the injury which determines management of care. Additionally, TBI severity can yield valuable insight about proximal and distal outcomes. It seems reasonable that it would be an important measure to include when examining the relationship between TBI and all included variables. Additional tools, such as the AIS scores and imaging studies, may be necessary in accurately capturing TBI severity in study participants; these studies, in addition to GCS, should be considered an essential variable that must be accounted for.

All of the studies measured presence of marijuana, yet the methods by which marijuana was measured varied. For example, urine was the most common way to measure marijuana concentration in patients in reviewed studies, but urine tests results are not specific to time of injury: The detectable level of marijuana can be present in urine for approximately 4.6 to 15.4 days after last use for infrequent and chronic users respectively. The presence of marijuana on a urine toxicology screen may not accurately reflect or correlate marijuana levels in an individual's system at time of injury, rather, it reflects recent use. Therefore, when considered as a variable, a marijuana level should be considered as reflective of recent use at time of injury, not directly at time of injury.

Finally, this review and other systemic reviews consistently identify blood alcohol concentration (BAC) as an important potential confounder in TBI studies. (Shahin & Robertson, 2012) All reviewed studies except (Nguyen et al., 2014) included alcohol as one of the examined substances. Much has been studied about the relationship between alcohol and TBI. As a prominent pre-disposing factor in TBI, the implications alcohol intoxication has on TBI is important and must be accounted for when examining the effects of marijuana on TBI.

Limitations

The current systematic literature review has several limitations, the first of which was the inability to perform a meta-analysis with the studies acquired. There was heterogeneity across the studies addressing marijuana exposure and TBI; from different criteria used to classify TBI, to diverse populations of interest, to varied outcomes of measures, the studies varied widely preventing a meta-analysis of the 8 included studies. Additionally, the studies differed in the type of data they collected, especially individual level data, which do not provide the necessary statistical measures that would make a meta-analysis meaningful.

The use of self-report methods, which can be susceptible to recall bias, a method utilized in the majority of the reviews included, poses another limitation. Future studies that integrate objective methods of measurement would be useful for confirming the presented results thereby enhancing comparability. Additionally, all 8 included studies were retrospective cross-sectional type studies; these types of study designs limit the ability of establishing causality and directionality of relationships as well as any inferred associations.

Conclusion

Traumatic brain injuries are a leading cause of mortality, morbidity, and disability in the U.S. (Taylor et al., 2003). Studies have shown that substance abuse, specifically alcohol, is present in up to 51% of individuals who have sustained a TBI when admitted to an emergency department (Corrigan, 1995; Parry-Jones, Vaughn, & Miles, 2006; Niemeier et al., 2016). The relationship between alcohol and TBI prevalence and outcomes have been well studied and documented (Niemeier, 2016). While it is known that there is significant alcohol use related to TBI, little is known about the influence of drug use, specifically marijuana, on the prevalence, severity and outcomes related to TBI (Andelic, 2010). Findings from this systematic literature review identified a significant knowledge gap regarding the relationship between marijuana and TBI. Only one study in this review specifically addressed this question and found that a positive marijuana screen was independently associated with survival after TBI, although findings are limited because of the retrospective nature of the study. This review identified the need for larger, better designed studies to address the significant knowledge gap about the relationship between marijuana use and its influence on TBI. Data and knowledge derived from such studies can help inform public policy and aid in the development of interventions that target prevention and increase awareness of TBI risk when under the influence of marijuana.

CHAPTER 3: CONCEPTUAL FRAMEWORK

Theoretical Orientation

As a trauma clinician, my theoretical orientation focuses on injury prevention and favorable outcomes in the context of severe trauma, especially TBI. Epidemiological observation shows that the landscape of TBI prevalence and outcome is changing, but there is not a good understanding of how, which would make visible actionable areas for beneficial intermediation. Therefore, this study orients to the phenomenon of TBI epidemiologically. The definition of epidemiology is the study of the distribution and determinants of diseases and injuries in human populations (Mausner & Kramer, 1985, p. 1). Epidemiological data includes data gathered via interviews, archival research, and record review as well as via direct observation. The unit of analysis in epidemiology is the individual, yet focuses on identifying factors that are deleterious to the public (Inhorn, 1995).

For the phenomenon of marijuana use, there are many reasons why individuals choose to use marijuana, either for recreational purposes or medicinal purposes. While the social aspects and context for marijuana exposure and use are important in and of themselves, potentially adverse clinical outcomes are equally as important and valid. Findings of this epidemiological study may uncover important demographic characteristics and health effects that warrant further study to help better understand the positive and negative effects of marijuana exposure in the context of traumatic brain injury. In summary, while the individual and social characteristics of marijuana use may be diverse and in need of study, findings from the literature review in Chapter 2 identified that these individuals as a collective group are potentially at more at risk for incurring an injury that could eventually lead to a TBI. Determining this risk and identifying

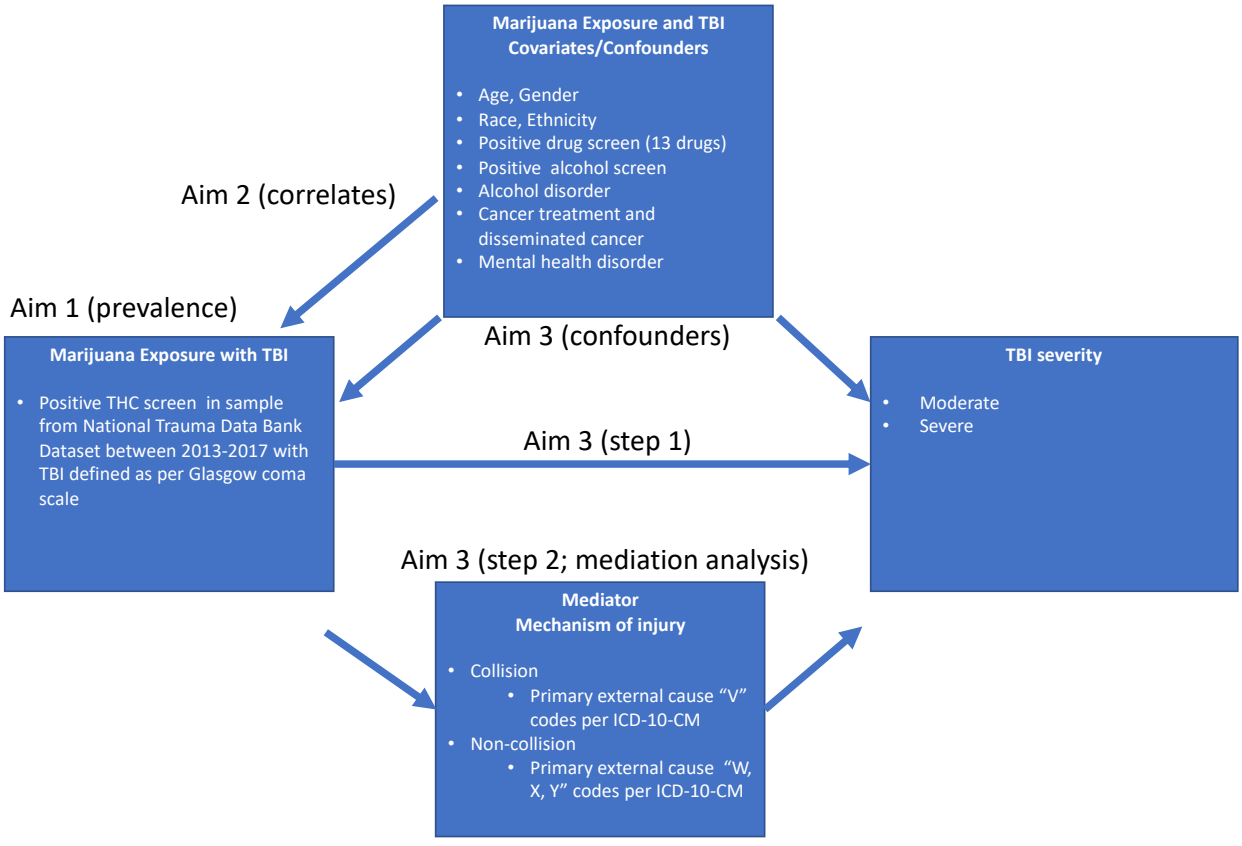
characteristics of the population that are potentially at greater risk than others is an appropriate focus for study.

Conceptual Framework

The systematic review conducted and reported in Chapter 2 identified the need for larger and better designed studies to address the significant knowledge gap about the relationship between marijuana exposure and its influence on TBI. To address the critical need, a conceptual framework has been developed for each of this study's aims, based on findings from the literature review and other existing knowledge about TBI. The framework is depicted in Figure 1, and the following sections will provide details on the justification for the model and included variables: Please see Chapter 4 for more details on each variable's operationalization.

Figure 2

Conceptual Framework for Study Aims



Sample: TBI patients

The sample will be extracted from the National Trauma Data Bank (NTDN) database from the years 2013-2017. The sample involves TBI patients, who will be defined in this study through a standardized evidence-based classification system, the Glasgow Coma Scale, that was developed by Teasdale & Jennett in 1974. TBI classification is a score of 12 or below on the Glasgow Coma Scale (GCS, range 3-15). Confirmation that a documented GCS accurately denotes the presence of an actual TBI will accomplished via ICD-9/10 codes. There are currently 8 ICD-9 code categories and 9 ICD-10 code categories that medically classify a brain injury. For details on codes see Section 4, Table 5.

Independent Variable: Marijuana Exposure

Marijuana exposure will be defined in this study as a positive drug screen for Tetrahydrocannabinol (THC) exposure via a urine sample. This screen is available in the NTDB.

Marijuana Exposure Correlates

A correlate is defined in this study as a characteristic of the marijuana-positive patient. Correlates were identified through the literature review (Chapter 2), other observational research, and clinical practice expertise. Identified correlates include age, gender, race, ethnicity, other substances, alcohol, alcohol use disorder, chemotherapy for cancer, disseminated cancer and mental/personality disorders. Age will be included because research has shown that certain age groups comprise of a larger percentage of current marijuana users (Substance Abuse and Mental Health Services Administration, 2018).

While no research has associated gender and ethnicity with marijuana use, they are both variables commonly studied in most observational research, therefore, it will be included in this study. Alcohol and other drug use at time of injury will be included in this study because research has shown that 1 in 8 individuals had both alcohol and an drug use disorder in the past

year (Substance Abuse and Mental Health Services Administration, 2018). Cancer dissemination and cancer treatment are included as correlates because studies show that smoked marijuana may be helpful in the treatment of nausea and vomiting because of chemotherapy (National Cancer Institute, 2019). Other studies have found that smoked marijuana may be beneficial in the treatment of neuropathic pain related to chemotherapy treatment (National Cancer Institute, 2019). Finally, mental illness will be included as a variable as Cannabis Use Disorder (CUD) is much higher in individuals with schizophrenia, personality disorders, post-traumatic stress disorder, mood and anxiety disorders, and other types of mental illnesses when compared to the general population (Lowe, Sasiadek, & Coles, 2018). Identified correlates were both identified and confirmed as extractable in the NTDB. There were no identified correlates that were NOT present in the NTDB. See Chapter 4 Table 6 for details about how each variable will be operationalized.

Mediator Variable: Mechanism of Injury

A mediator variable is the variable that causes mediation in the dependent and independent variables; for this study, marijuana exposure and TBI severity. A TBI occurs via injury, and the mechanism of injury is the mediator variable for this study. The leading causes of injuries resulting in TBI prevalence are collision related, such as motor vehicle crashes, or non-traffic related, such as falls. Mechanism of injury variables for this study include ICD-9/10 medical classification code categories for external causes of injury. See Chapter 4 Table 8 for details about each code to be used.

Dependent Variable: TBI Severity

TBI severity is defined per the GCS scale (Jain & Iverson, 2021). Moderate TBI is defined as a GCS score of 9-12 (range 3-15). Severe TBI is defined as a GCS score of 3-8.

Confounders

Confounding is a type of bias where a variable is associated with both the exposure and a given outcome resulting in a misrepresentation of the true relationship (Skelly, Dettori & Brodt, 2012). Confounding variables may conceal a true association, or they may falsely demonstrate an existent association between an intervention or exposure and an outcome when no association actually exists (Skelly, Dettori & Brodt, 2012). For this study, a confounder is defined as a variable that is associated with both the independent and dependent variable. Confounders were identified through the literature review (Chapter 2), other observational research, and clinical practice expertise. Identified confounders include age, gender, alcohol exposure at time of TBI, and alcohol use disorder, which is defined by the DSM-V as medical diagnosis indicating that the problem of drinking has become severe and chronic for the patient (National Institute on Alcohol Abuse and Alcoholism, n.d.). Physicians typically diagnosis this disorder through their history and physical assessment, which is documented in the patient's medical record and extracted into the NTDB by trained trauma program registrars. Participants' age as well as gender may be potential confounders, with males being at higher risk of sustaining a TBI (Vaarmo, 2014). Another potential confounder in this study is alcohol, or alcohol use disorder. There have been extensive studies conducted on the relationship between alcohol and TBI related outcomes, with alcohol identified in 35-50% of individuals who sustain a TBI (Corrigan, 1995; Parry-Jones, Vaughn, & Cox, 2006). Another confounding variable that will be examined is the use of other drugs. Evidence suggests that there is an increase in the presence of other drugs, aside from alcohol, in injured and fatally injured drivers (Asbridge, Hayden & Cartwright, 2012). Furthermore, findings from the literature review showed that the presence of other drugs in combination with marijuana was a common occurrence.

CHAPTER 4: METHODOLOGY

Study Design

A retrospective observational cross-sectional study design will be utilized. Observational studies can address a wide spectrum of clinical questions, especially in settings where a randomized controlled study might be difficult, unethical, or not feasible (Lu, 2009).

Setting

The setting involves trauma centers across the United States and Canada where patients who were diagnosed with moderate to severe TBI were treated. Included trauma centers are those that participate in the National Trauma Data Bank (NTDB) database submission. The NTDB is the most comprehensive national clinical database for traumatically injured patients currently available in the United States. The database captures data on 65% of all trauma centers in the U.S., comprising a representative sample of settings with hospitalized TBI patients.

Participants

Participants include individuals in the National Trauma Database that were diagnosed with a traumatic brain injury as defined by the National Trauma Data Base (NTDB). Please see section under 'Inclusion Criteria' for definitions.

Inclusion Criteria

Inclusion criteria includes patients in the NTDB database who are greater than or equal to 16 years of age who had sustained a moderate TBI (defined as GCS score of 9-12) or a severe TBI (defined as GCS score of less than or equal to 8).

Exclusion criteria

Patients that are not in the NTDB were excluded from this study, as there was no way to obtain data on them. Patients with a diagnosis of mild TBI were excluded because mild TBI patients mostly

experience only short-term symptoms, are not often hospitalized, and for the most part require significantly less treatments and care compared to moderate and severe TBI patients, who often have life-long and debilitating effects, and thus are the targets of public health initiatives (Centers for Disease Control, 2015). Patients under the age of 16 were not be included in this study because most marijuana users are between the ages of 18-25 years of age (Substance Abuse and Mental Health Services Administration, 2018).

Time Frame

The Trauma Quality Programs (TQP) research data housed in the NTDB for the years 2013-2107 is the time frame for this study. This time frame was selected because the TQP Participant User File does not report data after 2017 at this time, and 2013 marked the start of a revised data collection protocol for all participating trauma centers.

Data Source

The NTDB research dataset is available from the American College of Surgeons (ACS) through the Trauma Quality Program Participant Use File (PUF). The use file is a new addition by the ACS for trauma research and has replaced the previously available NTDB and is now the source of all informational and research purposes by the ACS.

Data Variables

Aim 1. For aim 1, the variables will include TBI and the presence of marijuana exposure in TBI patients. See Table 5 for operationalization of variables as specified in the NTDB data dictionary manual.

Table 5

Operationalization of Variables for Aim 1

Variable	Variable Type	How Operationalized in NTDB
Marijuana exposure	• Categorical • Binomial - Yes/No	• THC (Cannabinoid) element value is checked in 'Drug screen' section in NTDB dataset

TBI	• Categorical • Ordinal - moderate/severe	• GCS score 3-12
Confirmation of TBI categorization via GCS	• Categorical	• ICD-9/10 codes 800.1-800.39 (closed fracture of vault of skull with cerebral laceration and contusion); 800.6-800.89 (fracture of vault of skull); 801.1-801.39 (closed fracture of base of skull with cerebral laceration and contusion); 801.6-801.89 (fracture of base of skull); 803.6-803.89 (other and unqualified skull fractures); 804.6-804.79 (fractures with intracranial bleed); 851 (cerebral laceration and contusion, all); 852 (subarachnoid hemorrhage, subdural hemorrhage, extradural hematoma after injury, all) and 853 (other and unspecified intracerebral hemorrhage). International Classification of Disease, 10th Revision (ICD-10-CM) codes: S02.0xx (fractures of vault of skull); S02.1 (fractures of base of skull); S06.1 (traumatic cerebral edema); S06.2 (diffuse TBI); S06.3 (focal TBI); S06.31(contusion and laceration of right cerebrum); S06.32 (contusion and laceration of left cerebrum); S06.33 (contusion and laceration of cerebrum unspecified) and S09.x (unspecified intracranial injury).

Aim 2. For aim 2, the correlate variables will include patient characteristics identified through the systematic literature review. See Table 6 for details on how the variables will be operationalized.

Table 6

Operationalization of Variables for Aim 2

Variable	Variable Type	How Operationalized in NTDB
Age	• Continuous (may change to category based on scatterplot analysis)	• Reported as YYYY-MM-DD in the 'Date of Birth' section of the NTDB dataset • Patient's age at the time of injury documented (best approximation) in the 'Age' section of the NTDB dataset • Six units of measures defined as minutes, hours, days, months, years and weeks documented in the 'Age Units' section of the NTDB dataset
Gender	• Categorical • Binomial – Male/Female	• One of two value elements, male or female, will be selected in the 'Sex' section of the NTDB dataset
Race	• Categorical	• Six element values defined as Asian, Native Hawaiian or Other Pacific Islander, Other Race, American Indian, Black or African American, or White selected in the 'Race' section of the NTDB dataset
Ethnicity	• Categorical • Binomial – Hispanic or Latino/Not Hispanic or Latino	• One of two value elements, Hispanic or Latino, or Not Hispanic or Latino will be selected in the 'Ethnicity' section of the NTDB dataset

Drug screen	• Categorical	• Thirteen value elements present, all elements that apply will be selected for the first recorded positive drug screen results within 24 hours after first hospital encounter in the 'Drug Screen' section of the NTDB dataset • Drugs include: amphetamine, barbiturate. Benzodiazepine, cocaine, meth-amphetamine, ecstasy, methadone, opioid, oxycodone, PCP, tricyclic antidepressant, not tested, other
Alcohol	• Categorical • Binomial – Yes/No	• One of two data elements, yes or no for the blood alcohol concentration test performed within 24 hours after first hospital encounter will be selected in the 'Alcohol Screen' section of the NTDB dataset
Alcohol Use Disorder	• Categorical • Binomial – Yes/No	• One of two data elements, yes or no, for any descriptors documented in the medical record consistent with the diagnostic criteria of alcohol use disorder OR a diagnosis of alcohol use disorder documented in the patient's medical record will be selected in the 'Alcohol Use Disorder' section of the NTDB dataset.
Currently receiving chemotherapy for cancer	• Categorical • Binomial – Yes/No	• One of two data elements, yes or no, for patients who are currently receiving any chemotherapy treatment for cancer prior to injury will be selected in the 'Pre-existing Conditions' section of the NTDB dataset
Disseminated Cancer	• Categorical • Binomial – Yes/No	• One of two data elements, yes or no, for patients who have cancer that has spread to one or more sites in addition to the primary site AND in whom the presence of multiple metastases indicates that the cancer is widespread, fulminant, or near terminal will be selected in the 'Pre-existing Conditions' section of the NTDB dataset
Mental/Personality Disorders	• Categorical • Binomial – Yes/No	• Mental/Personality Disorders; one of two data elements, yes or no, for history of a diagnosis and/or treatment for the following disorder(s) documented in the patient's medical record: Schizophrenia, bipolar disorder, major depressive disorder, social anxiety disorder, posttraumatic stress disorder, and antisocial personality disorder will be selected in the 'Pre-existing Conditions' section of the NTDB dataset

Aim 3. For aim 3, the analysis will include the mediator variable of mechanism of injury, the confounding variables identified via literature review, and correlate covariates identified in aim 2 as potentially influencing the relationship between independent variable (marijuana exposure) and TBI severity. See Table 5 for operationalization of TBI severity variable. See Table 6 for operationalization of correlates that may serve as covariates in Aim 3. See Table 7

for operationalization of identified confounding variables. See Table 8 for operationalization of mechanism of injury variables.

Table 7

Operationalization of Confounding Variables for Aim 3

Confounding Variable	Variable Type	How Operationalized in NTDB
Age	• Continuous (may change to category based on scatterplot analysis)	• Reported as YYYY-MM-DD in the 'Date of Birth' section of the NTDB dataset • Patient's age at the time of injury documented (best approximation) in the 'Age' section of the NTDB dataset • Six units of measures defined as minutes, hours, days, months, years and weeks documented in the 'Age Units' section of the NTDB dataset
Gender	• Categorical • Binomial – Male/Female	• One of two element values, male or female, will be selected in the 'Sex' section of the NTDB dataset
Alcohol	• Categorical	• One of two element values, 'yes' or 'no' in the 'alcohol screen' section of the NTDB dataset
Alcohol Use Disorder	• Categorical • Binomial – Yes/No	• One of two data elements, yes or no, for any descriptors documented in the medical record consistent with the diagnostic criteria of alcohol use disorder OR a diagnosis of alcohol use disorder documented in the patient's medical record will be selected in the 'Alcohol Use Disorder' section of the NTDB dataset.
Drug screen	• Categorical	• Fifteen value elements present, all elements that apply will be selected for the first recorded positive drug screen results within 24 hours after first hospital encounter in the 'Drug Screen' section of the NTDB dataset

Table 8

Operationalization of the Mediator Variable of Mechanism of Injury

Mediator Variable	Variable Type	How Operationalized in NTDB
Mechanism of injury: collision	• Categorical	• ICD-9 code categories: E800-E807; E810-E819; E820-E829; E830-838; E846-E848 • ICD-10 code categories: V00-V99
Mechanism of injury: non-collision	• Categorical	• ICD-9 code categories: E880-E929; E950-E9999 • ICD-10 code categories: X00-Y09; Y21-Y99

Data Cleaning Procedures

The first phase of the data cleaning process will be data screening. When screening data, four types of abnormalities will be assessed: (1) missing data, (2) inconsistences and outliers, (3) odd patterns of distributions, and (4) unexpected analysis results, inferences or abstractions (Van den Broeck, Cunningham, Eeckels, & Herbst, 2005). Descriptive tools, such as Statistical Package for the Social Sciences (SPSS) will be utilized to facilitate the screening process and ensure the process is objective and systematic. A potential source of problem in this study that may be encountered during data collection is missing data, outliers, and inconsistencies due to the use of a database that includes existing data that was not specifically collected for the purposes of this study. Errors such as blank fields, unintentional deletions or duplications during data entry, blank data fields, or values incorrectly entered must be accounted for (Van den Broeck, Cunningham, Eeckels, & Herbst, 2005). Screening methods involving graphical exploration of distributions and statistical outlier detection will be utilized.

The second phase in the data cleaning process is the diagnostic phase. In this phase, a diagnosis regarding the nature of concerning data points or patterns will be attempted. Potential diagnoses for each data point include the following: erroneous, true normal, true extreme, or idiopathic (Van den Broeck, Cunningham, Eeckels, & Herbst, 2005). The correct value or data point for certain fields can be obvious and easily noticed (e.g., if a value for an individual's age was entered as 223 rather than 23). For such erroneous or missing data points, processes regarding dealing with missing data will be implemented and corrected prior to analysis.

The treatment phase of identified erroneous data involves correcting, deleting or leaving the error unchanged (Van den Broeck, Cunningham, Eeckels, & Herbst, 2005). For purposes of this study, if impossible or missing values are observed, they will have to be deleted, as there would be no way of correcting that value related to the retrospective and secondary nature of the

data. For data points that are true extremes, further examination on the influence of these data points, individually and collectively, on analysis will be made prior to determining whether or not that data point will be deleted or left unchanged (Van den Broeck, Cunningham, Eeckels, & Herbst, 2005).

Dealing with Missing Data

Identifying Missing Data. It is important to deal with missing data because missing data can create bias. First, an exploratory analysis will be performed to look at frequencies or percentages of missing data, and to help identify how much data is missing. Next, an analysis of the mechanisms, or types, of missingness will be performed to identify whether the missing data is missing completely at random (MCAR), missing at random (MAR), or not missing at random (NMAR) using statistical tests, such as Little's test for MCAR. Following this, an analysis for patterns of missingness will be performed using a missing pattern value chart. There are two patterns that may be potentially observed: 1) a monotone pattern where data is missing systematically, or 2) an arbitrary pattern where data are missing at random (Salgado, Azevedo, Proença, & Vieira, 2016). While the analyses are not definitive, they can bring attention to blatant anomalies in the missingness of data and help to make decisions on the missing data handling procedures.

Handling Missing Data. There are a variety of methods that can be utilized to deal with missing data. The type of method utilized will depend on the percentage of missing data present and cannot be specified beforehand. Simple methods, such as listwise or pairwise deletion are helpful when the percentage of missing data is less than 5%. Listwise deletion, also known as complete-case analysis, removes all data for a case with one or more missing values. In other words, that case is omitted completely. A disadvantage when using listwise deletion is that it can

reduce the sample size. On the other hand, pairwise deletion, also known as available-case analysis, aims at minimizing the loss of other potential data incurred with listwise deletion. Pairwise deletion still uses that case when analyzing other variables with non-missing values; it just excludes that one value with a missing data. An advantage to pairwise deletion over listwise is that it can help increase statistical power. However, pairwise deletion does have its disadvantages in that most software packages use the average sample size across analyses which can create over or underestimation.

If the percentage of missing data is greater than 5%, then more advanced methods of dealing with missing data can be utilized, such as imputation. Imputation methods will depend on the pattern of missingness identified and the type of variable requiring imputation (continuous, ordinal, or nominal). In patterns where missing data is systematic or monotone, methods such as regression, predicted mean matching or propensity scoring are helpful. In patterns where missing data is arbitrary or at random, methods such as multiple imputation using maximum likelihood regression methods to predict missing values based on observed values and sensitivity analyses that simulate the results based on a range of plausible values can be used.

Power Analysis

An a priori sample size calculation was done using an anticipated effect size of .10, a power of .8, a probability level of .05 and 10 covariates, which includes listed confounders in table 7 and a decision of 6 correlates that via analysis may be included in the logistic regression. The minimum required sample was 172. The database currently has more than 7 million electronic records (NTDB, 2016). For 2016 alone there were 861,888 records submitted by 747 facilities (NTDB, 2016). Although it cannot be determined a priori the count of TBI patients in the database, 30% of trauma related injuries

are TBI, hence it can be safely assumed that for 2017 alone there will be 300, 000 potential eligible participants, meaning enough participants are available to conduct all study analyses.

Data Analysis

Aim 1. For Aim 1, the objective is to determine the prevalence of marijuana exposure in patients with moderate or severe TBI. Analyses will be conducted using the Statistical Package for the Social Sciences (SPSS) software. The proportion of TBI patients who have marijuana present on admission will be reported. Unadjusted prevalence will be determined through a 2x2 table. Prevalence rates will be calculated for total number of TBIs.

Aim 2. For Aim 2, the objective is to determine the correlates associated with the presence of marijuana exposure at the time of injury. The correlates included in Aim 2 will be also collected for the sample of participants without marijuana exposure at time of injury. Measures of central tendency, including range, means, proportions and standard deviations will be calculated. These basic summary statistics will be calculated for continuous variables (age) and binary categorical variables (gender, race, ethnicity, drug screen, alcohol, alcohol use disorder, chemotherapy, disseminated cancer, mental/personality disorders). Continuous variables will be plotted to assess for normality; tests to assess for normality will include kurtosis and skewness. If data is normally distributed, then parametric statistics will be utilized. If data is not normally distributed, then non-parametric statistics will be utilized. Frequency distributions, including numbers and percentages, will be generated for each of the categorical variables/correlates; scatterplots will be created so that outliers can be identified.

All correlate variables presented in table 6 will be examined; all the variables but one are categorical variables. Categorical variables will be mapped against presence of marijuana exposure and TBI severity to determine if significant differences are present across each of the categories. Tests to determine significant differences across categories include chi-square test or Fisher's exact test based on

the data. Variables that are identified as significant will be used as covariates in the adjusted prevalence rates. The variable of age is a continuous variable. The literature suggests that the relationship between age and drug exposure is not linear so we will test this relationship in this study. For this study a bar plot graph plotting age against marijuana exposure will be used to determine if a linear relationship exists. If there is not a linear relationship, the variable will be categorized. Correlates that are identified as significant will become covariates in the adjusted prevalence analysis. Prior to the adjusted prevalence analysis, these covariates will be examined for multi-collinearity.

Aim 3. For Aim 3, the objective is to determine the relationship between marijuana exposure at the time of injury, the mechanism of injury, and TBI severity. The null hypothesis is that a relationship between marijuana at the time of injury, the mechanism of injury, and severity of TBI does not exist. As illustrated in the conceptual framework (see Figure 2), mechanism of injury is considered a mediating variable; it potentially mediates the relationship between marijuana exposure at time of injury (independent variable) and TBI severity (dependent variable). First an estimate of the effect between marijuana exposure and TBI severity will be obtained without the mediator variable of mechanism of injury. To test for mediation, several regression analyses will be conducted that include the mediator variable and significance of the coefficients will be examined in each step to assess for direct and indirect effects. First, I will test for a direct relationship between marijuana exposure and TBI severity. Assuming there is a significant relationship between the two variables, I will then conduct an analysis to determine if marijuana exposure affects mechanism of injury. Assuming there is a significant effect, I will then conduct an analysis to determine if mechanism of injury affects TBI severity, and whether the mediation effect is complete (the effect of marijuana exposure completely disappears) or partial (the effect of marijuana exposure is reduced). To determine if the mediation effect is statistically significant (assuming there is not a complete mediation effect) I will use either the Sobel test (Sobel 1982) or

bootstrapping methods (Preacher & Hayes, 2004). All analyses will be conducted unadjusted and then adjusted for covariates and confounders identified a priori and via aim 2 (see Figure 2).

The analyses will use logistic regression modeling because the dependent variable, TBI severity, is a dichotomous variable with only two choices, moderate or severe TBI. While TBI severity can be considered a continuous variable if using the number scoring of the GCS scale, a binary variable will be used as it is easier to interpret for clinicians using a numerical score: clinicians treat not on subtle degrees of TBI severity, but whether it is a moderate or severe one based on GCS threshold cut-offs.

Dummy variables will be used to input non-binary categorical variables into the analysis. However, with the predicted large sample size, and understanding the potentially significant confounding effects of certain variables such as other drugs, I hope to create binary variables for each drug listed in the NTDB database (13 in all). But if this is unable to be done another approach would be to code all drug use into 3 categories: a value of 0 assigned for 'no drug use', a value of 1 for 'stimulants' only (e.g., amphetamines and meth-amphetamines, and a value of 2 for all 'depressants' (e.g. opioids and oxycodone).

Potential Study Biases as Study Limitations

Observational studies offer valuable methods for studying various problems within healthcare where other study design methods, such as randomized controlled designs (RCTs), may not be feasible or even unethical. High quality observational studies can render invaluable and credible results that positively impact healthcare when studying clinically relevant topics in patient populations of interest to practicing clinicians. Despite this, observational studies can be subject to a few potential problems within the design and analytical phases rendering results highly compromised. Potential problems that will be encountered in this study design are selection bias, information bias and confounding. Possible countermeasures to address these problems will be discussed in this section.

Selection bias. A potential problem regarding selection bias is present in the current study. The target study population is comprised of a purposive sample of patients registered in the NTDB. The NTDB is a centralized national trauma registry developed by the American College of Surgeons (ACS) with the largest repository of trauma related data and metrics reported by 65% of trauma centers across the U.S. and Canada. The main advantage to utilizing such a registry for this study is that it constitutes the largest trauma database in the U.S. Furthermore, the NTDB allows for risk-adjusted analyses which can be important when evaluating outcomes in trauma (Haider et al., 2012). Despite its incredible potential in informing trauma related research, the selection of participants from the NTDB is not without its own biases.

The reporting of data into the NTDB is done on a voluntary basis by participating trauma centers, rendering a convenience sample that may not be representative of all trauma patients, and may also not be representative of all trauma centers across the U.S. (Haider et al., 2012). This creates the problem of selection bias. Furthermore, the NTDB is subject to the limitations of selection bias is that it includes a larger number of trauma centers with typically more severely injured patients potentially underrepresenting patients with milder traumatic injuries and injury scores (NTDB, 2016). Additionally, patients who may be traumatically injured and who are not admitted to a participating trauma center will not be included in the NTDB, nor will trauma patients who died on scene before being transported. Another consideration to note is that participating hospitals may differ in their criteria of which patients to include in the database, specifically patients who are dead on arrival or those who die in the Emergency Department (NTDB, 2016). This discrepancy in inclusion and exclusion criteria between hospitals regarding specific injuries makes representative comparisons potentially difficult. Lastly, it is important to mention that large databases such as the NTDB are subject to missing data or disparate data. This is often due a multitude of factors, a few of which various demographic data points, test

results and other key information, such as procedures, that may not be documented in the health record and therefore omitted in the database (Mack, Su, & Westreich, 2018). Missing data often contributes to information bias; however, it can also contribute to selection bias because one of the methods in dealing with missing data is excluding participants for which data is missing thereby creating potential selection bias. Missing data may undermine the ability to make valid inferences, therefore, steps will be taken throughout the design and operational stages and methods within this study to avoid or minimize missing data. Methods to reduce information bias that can lead to selection bias will be discussed in the analysis section of this paper.

Informational bias. Due to the methods by which data are collected and inputted into the NTDB, potential problems are encountered in terms of data accuracy. Underreporting of variables obtained from the NTDB has often been noted as a problem due to the reliability of data extraction by participating hospitals (Kardooni et al., 2008). The data is self-reported and often inputted by staff dedicated to data collection. A major variance between participating hospitals is that hospitals with more resources are more likely to have dedicated staff to data collection. This can lead to informational bias in those hospitals that are more compliant in reporting data metrics when compared to others that are not. For example, hospital data registries that have incomplete data on complications may appear to deliver better care than hospitals that consistently record all complications. A recent study by Arabian et al. (2015) revealed the presence of inaccuracy and variability between hospitals, specifically in the areas of data coding and injury severity scoring. Additionally, the type of registry software a hospital utilizes can report injury severity scores differently (NTDB, 2016). This too, renders data subject to informational bias.

Information bias is due to inaccurate or incorrect recording of individual data points. When continuous variables are involved, it is called measurement error; when categorical variables are

involved, it is called misclassification (Hammer, du Prel, & Blettner, 2009). In this study, the potential for information bias is mostly due to 1) incomplete data documented in the medical record, or 2) inaccurate entry into the hospital trauma database by hospital staff. Missing data will be analyzed in terms of potential effect for both the independent (the presence of marijuana at time of injury) and dependent variable (TBI severity).

While the database captures marijuana exposure through the first recorded positive drug screen within the first 24 hours after first hospital encounter, it is recognized that at times patients will not be screened, even if they have been exposed to marijuana. Marijuana exposure is identified through the presence of Cannabinoid (THC) in a urine toxicology screen. Marijuana presence can be detected in the urine up to 3-5 days from exposure in infrequent users; marijuana can be detected up to 30 days for chronic users (Mayo Clinic Laboratories, 2019). Therefore, patients could potentially have a positive marijuana toxicology screen even though they may not have ingested marijuana the day of the event. A positive marijuana urine toxicology screen indicates the probability of prior use, not immediate use. This is an important limitation to note. In clinical practice, the determination for a toxicology screen is often symptomology, so it is reasonable to assume that patients who have ingested marijuana a week prior to the event date may not exhibit the expected symptomology.

Unlike other observational cohort studies, the potential of recall bias is minimal due to the availability of an objective marker to measure the independent variable, namely, the presence of marijuana. The presence of marijuana is captured from the hospital lab urinalysis results and is recorded as present within 24 hours after the first hospital encounter. Similarly, the data entered to measure the GCS score is also captured objectively through a numeric recorded score found in the medical record. See analysis section for how this type of bias will be addressed.

Confounding. Confounding is a type of bias where a variable is associated with both the exposure and a given outcome resulting in a misrepresentation of the true relationship (Skelly, Dettori & Brodt, 2012). Confounding variables may conceal a true association, or they may falsely demonstrate an existent association between an intervention or exposure and an outcome when no association exists (Skelly, Dettori & Brodt, 2012). Participants' age as well as gender may be potential confounders, with males being at higher risk of sustaining a TBI (Vaarmo, 2014). Another potential confounder in this study is alcohol. There have been extensive studies conducted on the relationship between alcohol and TBI related outcomes, with alcohol identified in 35-50% of individuals who sustain a TBI (Corrigan, 1995; Parry-Jones, Vaughn, & Cox, 2006).

CHAPTER 5: RESULTS

Data Source

The NTDB research dataset is available from the American College of Surgeons (ACS) through the Trauma Quality Program Participant Use File (PUF). The use file is a new addition by the ACS for trauma research and has replaced the previously available NTDB and is now the source of all informational and research purposes by the ACS.

Sample Size

The final sample size for this study involved 7,875 total unique cases. Those cases represent individuals who sustained a moderate or severe TBI in the NTDB database. Of the 997,970 total cases for 2017, there was a total of 32,896 cases that were identified as having sustained some form of traumatic brain injury, ranging from a concussion to severe injury, using the ICD 10 Diagnosis codes listed below (see data cleaning section). Of the 32,896 cases, 25,021 were identified as having a concussion diagnosis, and were ultimately excluded from the final sample size. This was because mild concussion diagnosis was found to suffer from large underestimates in documented incidence (Leo & McCrea, 2016). A World Health Organization (WHO) systematic review of mild TBI found that up to 90% of overall TBIs was mild in nature. The WHO has also estimated a yearly incidence of mild TBI (i.e., concussion) anywhere from 100-600 per 100,000 cases, 0.1 to 0.6 respectively (Leo & McCrea, 2016). Furthermore, up to 40% of individuals who sustain a mild TBI, or concussion do not seek the attention of a physician (Demakis & Rimland, 2010). Another study found that 57% of veterans who had returned from Iraq and/or Afghanistan, and had sustained a possible TBI, were not evaluated or seen by a physician (Tanielian & Jaycox, 2008). According to the WHO and CDC reports, these numbers may still not represent the actual incidence of TBI worldwide. Furthermore, the data suggests that individuals with a mild TBI (i.e., concussion) for the most part do not go and seek medical attention, and this study

focuses on individuals who sustain a moderate or severe TBI as those individuals suffer life-long devastatingly debilitating effects and are the targets of public health initiatives and injury prevention measures.

Time Frame

The Trauma Quality Programs (TQP) research database housed in the NTDB for the year 2107 is the time frame for this study. Though initially the researcher intended to include data from 2013-2017, data from years other than 2017 had to be excluded. In effort to standardize the type of data collected by local, regional, and state trauma registries, the NTDB designs a National Trauma Data Standard (NTDS) Data Dictionary that is designed to establish a national standard for the collection of trauma registry data while also providing the operational definitions for the NTDB. In summary, the NTDS provides the exact standards for trauma registry data submitted to the NTDB. Prior to the 2017 data dictionary, trauma registry programs had limited selections regarding data related to drug use. The options provided by the NTDB registry only included whether drug use was present (yes or no) and whether it was confirmed by a test or by prescription. It did not allow the trauma data abstractor to specifically identify the type of drug found. In 2017, the data dictionary was revised to include a drug screening category that aimed at recording the first positive drug screen result within 24 hours after the first hospital encounter. Typically, in trauma hospitals reporting to NTDB and within the context of trauma, acquisition of a urine and blood drug and alcohol screen is standard expectation of practice. It then provided a list of 15 options for the abstractor to choose from. Because it was impossible to isolate cannabinoid use in earlier data sets, the researcher was only able to use the 2017 NTDB data set, which at the beginning of the study was the latest available data set by the NTDB. As of February 13th, 2021 the 2018 NTDB data set was not available.

Data Storage

Access to the dataset was approved by the American College of Surgeons, and a Participant Use File (PUF) link was sent to the researcher via direct email. The file was uploaded and stored on a private, password protected computer. Data from the CSV file was also uploaded to a protected SPSS version 25 portal via the University of California, Irvine school portal via the Apporto program.

Dataset Merging

All the trauma data used in this study are organized by an element INC_KEY, which is a designated unique identifier for each record. The designated unique identifier INC_KEY expresses a unique clinical visit/episode by an individual at a participating trauma center. It is important to consider that an individual could have been included/counted more than once in the registry because of more than one traumatic event within the year. The Participant Use File (PUF) Trauma data set contained all the demographic, environmental, and clinical data information. However, it did not identify or delineate TBI cases as such. Therefore, a separate data set that contained ICD 10 Diagnosis Codes had to be utilized to identify TBI cases which then could be used to create a merged data set that is complete.

The 2017 PUF Trauma data set was uploaded to SPSS version 25 on September 10th, 2020. The PUF Trauma data set included a total of 997,970 unique identifier cases. A frequency analysis was performed to ensure no duplicate cases were found (i.e., each row designated a unique visit). The PUF Trauma data set included 328 unique variables.

Next, the PUF ICD-10 Diagnosis data set was uploaded and examined. The PUF ICD Diagnosis data set is organized via the same INC_KEY identifiers. The PUF ICD Diagnosis data set included 3 variables: ICD CM diagnosis code, ICD CM diagnoses code Blank Inappropriate Values (BIU) and ICD Clinical Modification version. This data set was used to distinguish TBI cases from cases related to

other traumas such as pneumothorax, liver laceration or femur fractures. The way this was done was first the researcher identified TBI related ICD 10 CM diagnosis codes by visiting the ICD 10 Data website at www.icd10data.com and searching for all head injury related codes. Additionally, the selection of TBI related ICD 10 codes was corroborated by examining a list of codes found in existing studies on TBI which validated the inclusion of the specifically identified TBI codes in this study. Though these other studies included ICD 10 Diagnosis codes related to concussion injuries (S06.0 concussion), these codes were excluded from this study as the researcher was only interested in identifying cases with either a moderate or severe TBI and concussions are designated as mild TBI.

The following codes were ultimately selected: S02.0xx (fractures of vault of skull); S02.1 (fractures of base of skull); S06.1 (traumatic cerebral edema); S02.19XD (Other fracture of base of skull) ;S06.2 (diffuse traumatic brain injury); S06.30 (focal traumatic brain injury); S06.31 (contusion and laceration of right cerebrum); S06.32 (contusion and laceration of left cerebrum); S06.33 (contusion and laceration of cerebrum, unspecified); S09.X (unspecified intracranial injuries of the head). Next, PUF ICD 10 Diagnosis codes were regrouped into the following categories via numerical representation. ICD 10 Diagnosis code S02.0xx was grouped into group 3683-3687; S02.1 into group 3688; S02.19XD into group 3738; S06.1 into group 4008-4025; S06.2 into groups 4026-4045; S06.3, S06.31, S06.32, and S06.33 into groups 4046-4095; S09.X into groups 4310-4311.

A missing value analysis for the ICD 10 Diagnosis code variable revealed no missing values. A new variable titled ‘TBI” was created in the PUF ICD-10 Diagnosis data set where if a TBI related ICD 10 code was assigned, the value ‘1’ was given. If not, it was assigned a value of ‘0’. A frequency analysis on the ‘TBI’ variable was then done to determine the number of TBI codes which were found to be 131,518.

The PUF ICD 10 Diagnosis code data set was then merged with the main PUF Trauma data set to create a new data set that can identify TBI cases where the unique identifiers were labeled as TBI or not. A frequency analysis on the 'TBI' variable in the 'PUF Trauma Merged' data set was done to ascertain how many TBI cases were found. Of the 997,970 total cases, 7,875 unique TBI cases were identified. That comprised 0.8% of the total cases within the 2017 PUF Trauma data set. While this may seem to be a smaller number, it is important to consider that there is no one system that tracks the occurrence of TBIs in a large population both in the United States and worldwide (Laskowitz D, Grant G, editors. Boca Raton (FL): CRC Press/Taylor and Francis Group; 2016.) The CDC uses the GCS as the main tool to classify TBI severity, but in doing so, it overestimates the number of TBI, which is why it recommends using a separate criteria tool in conjunction to GCS. Other recommended criteria tools would be duration of altered mental status, post-traumatic amnesia or structural damage identified on CT scan (Report to congress 2015). Because the presence of post-traumatic amnesia is not found as a variable in this data base, as well as evidence of structural damage identified on CT, the ICD 10 Diagnosis codes were selected in this study as one of two criteria to identify TBI cases and determine overall severity. See Table 9 for frequency analysis results. To facilitate further data cleaning and analyses, a new data set was created whereby only the 7,875 TBI cases were represented. This new data set was called 'PUF Trauma TBI Only'.

Table 9

Frequency Table for Original Data Set

	Frequency	Percent	Valid Percent	Cumulative Percent
Non-TBI	990095	99.2	99.2	99.2
TBI	7875	0.8	0.8	100

Total	997970	100	100

Final Data Set

Variables

The final data set to be used in the analysis consisted of 15 variables not including the cases themselves: *sex*, *age in years*, *race* (concatenated), *ethnicity*, *alcohol screen result*, *total GCS*, *cannabinoids* (concatenated and restructured), *positive for drugs* (concatenated and restructured), *comorbid condition currently receiving chemotherapy*, *comorbid condition disseminated cancer*, *comorbid condition mental/personality disorder*, *comorbid condition substance abuse disorder*, *comorbid condition alcohol use disorder* (restructured), *crash intrusion* and *motorcycle crash*.

The new data set contained 324 total variables. The variables present were identified as subsets of the following categories: work-related injury, patients occupational industry, patient's occupation, ICD 10 primary external cause, ICD 10 place of injury code, ICD 10 additional External cause code, protective devices, child specific restraint, airbag deployment variables, report of physical abuse, investigation of physical abuse, caregiver at discharge, transport modes, initial emergency service system (EMS) vital signs (blood pressure, pulse, respiratory rate, oxygen saturation, GCS), time to EMS response, time from dispatch to ED/hospital, interfacility transfer, pre-hospital cardiac arrest, trauma center criteria for admission, vehicular/pedestrian or other risk, mechanism of injury (e.g. falls, vehicular, pedestrian, other risk, crash intrusion), total time between ED/hospital arrive and ED discharge, systolic blood pressure, pulse rate, temperature, respiratory rate and assistance, pulse oximetry, supplemental oxygen, height, weight, primary method of payment, signs of life, emergency room disposition, hospital

discharge disposition, comorbid conditions (except for alcohol use disorder, disseminated cancer, receiving chemotherapy, and substance abuse), total intensive care unit length of stay, total ventilator days, length of stay (days), hospital complications, procedural interventions, medications administered, blood transfusions, withdrawal of life support, facility level, year of discharge, ISS, and AIS derived ISS.

Variables that would not be included in the final analysis were removed. Example of variables removed were ventilator days, length of stay and blood transfusions. Some of the variables that incorporated more than one value, such as *race*, *ethnicity*, *alcohol screen result* and *drugs*, were concatenated to form new variables. A description of how each variable was dealt with is delineated below. This was done to facilitate the analysis of more than one categorical variable to be treated as one.

Missing Value Analysis

In SPSS the missing values analysis module provides two different methods to analyze missing data, the first is the Expectation-Maximization method and the second is the Regression Imputation method (SPSS, 2000). Expectation-Maximization provides statistical estimates such as estimated means, covariances and correlations. The Regression Imputation method is dependent on the Expectation-Maximization method to fill in the missing values using predicted values from a regression of one variable on another within the analysis (SPSS, 2000). Both analyses were performed to assess any patterns of missing values.

A missing value analysis was conducted. This analysis produces a univariate statistics table showing the total number of cases within each variable, the mean and standard deviations, the missing counts and percentages and the number of extremes. It is here that the extent of missing data can be observed and identified. For this data set, the analysis revealed a mean for *age in*

years (*M* = 33.78; *SD* = 27.35), *total GCS* (*M* = 13.65; *SD* = 3.423) and *alcohol screen result* (*M* = .0622; *SD* = .111). It also displays the count and percentages for the following variables with missing values: *age* (2303, 29.2%), *alcohol screen result* (5788; 73.5%), *total GCS* (494; 6.3%), *sex* (3, 0.03%), *race* (195, 2.3%), *ethnicity* (543, 6.9%), *THC Combo* (5814, 73.8%), *positive for drugs new* (0, 0%), *comorbid condition currently receiving chemotherapy for cancer* (0, 0%), *comorbid condition disseminated cancer* (0, 0%), *comorbid condition mental/personality disorder* (0, 0%), *comorbid condition substance abuse disorder* (0, 0%), and *comorbid condition alcoholism* (0, 0%), *mechanism of injury motor vehicle collision* (0, 0%), and *mechanism of injury motorcycle crash* (0,0%)

Separate-Variable *t* Test. A separate-variance *t* Test table is displayed by SPSS as part of the missing value analysis. This table can help identify variables whose pattern of missing values may be influencing the quantitative variables. When *age* is missing, the mean *alcohol screen result* is .0031 compared to .0652 when *age* is present. This large difference in mean *alcohol screen result* scores when *age* is present indicates that the data missing is not missing at random. When *age* was missing, mean *total GCS* was 14.77 compared to 13.21. This is not a large difference, indicating that data may be indeed missing at random.

When *alcohol screen result* is missing, the mean *age* is 28.86 compared to 42.64 when *alcohol screen result* is present. This indicate that the data may not be missing completely at random it is important to consider that in the *alcohol screen result* variable, there is a large percentage of missing values. Additionally, since this data set includes patients ages 16 years and younger, it may be that clinicians are not drawing alcohol levels. This can lead to the fact that the values that are missing when these two variables are cross-tabulated, may not be missing at random. Finally, it is important to note that unlike in questionnaires or surveys, these trauma

patients are not asked for an alcohol screen result, rather they are tested by the retrieval of a blood sample. Therefore, it is not the patient themselves that chooses to respond or not, rather, it is the hospital system that contributes to whether the data is missing. Data for *alcohol screen result* may be missing due to lack of time to retrieve the blood sample as can be found when patients present to the ER in traumatic full arrest. Alternatively, the sample may have been drawn but not sent to lab, or sent to lab but not reported by lab, or reported by lab not recorded by the nurse. All these clinical scenarios are suggested to contribute to the high number of missing data, and as can be seen in further analyses, seems to be missing at random. Furthermore, when *alcohol screen result* was missing, mean *total GCS* was 14.13 compared to 12.38 when *alcohol* was present. This difference is indicative that the data is not missing at random.

When *total GCS* scores were missing, the means for age and alcohol screen result also differed, but less so. When *total GCS* was missing, mean *age* was 31.47 compared to 33.89 when *total GCS* was present. Similarly, mean alcohol *screen result* was .0720 when *total GCS* was missing compared to .0620 when it was present. The mean *total GCS* when *age* was missing was 31.47 compared to 33.89. When alcohol was missing was 13.05 compared to 12.22 when alcohol was present. The difference is small which may indicate that the data is indeed missing at random.

The means for *age*, *alcohol*, and *total GCS* were very similar when *ethnicity* was missing or present. Mean age was 33.42 when *ethnicity* was missing compared to 33.80 when it was present. Mean *total GCS* was 13.17 when *ethnicity* was missing compared to 13.69 when present. Similarly, the mean *alcohol screen result* was .0503 when *ethnicity* was missing compared to .0631 when present. This indicates the data is missing at random.

Lastly, the means for *age* and *total GCS* differed in the presence of *THC*. When *THC* was missing mean *age* was 31.17 compared to 39.49, mean *total GCS* was 14.03 compared to 12.62 when *THC* was present. Alternatively, the means for *alcohol screen result* were similar in the presence or lack thereof of *THC*. When *THC* was missing, mean *alcohol screen result* was .0615 compared to .0628 when present. As explained above, the larger difference in means may indicate that the data missing is not missing completely at random. However, it is important to consider that these differences cannot be solely attributed to the patient's provision of information, as these are all clinical tests performed by hospital personnel. If data is missing, it is most likely due to the reasons mentioned above, and not necessarily because the patient was choosing to withhold information.

Crosstabulation of Categorical Variables. The crosstabulations of categorical variables versus indicator variables table shows similar information to that found in the separate-variance *t* test table. This table provides information that can help determine whether there are differences in missing data among different categories. Males were found to have a documented value in alcohol screen 30.4% compared to 19.3% in females. This may indicate that there are differences in missing values among males and females. Similarly, males were found to have a documented *THC* result 28.4% of the time compared to females at 22.1% of the time. This indicates that the data is missing at random. Differences were smaller between males and females for the variables of *total GCS* and *ethnicity*, with males having a documented result for *total GCS* 94% of the times compared to 93.1% for females. *Ethnicity* was documented for 93.2% of the times with male participants and 92.9% for females. The small difference indicates that the data is not missing at random.

For the variable of *race*, no drastic differences were noted between *ethnicity*, and *THC Combo*. However, the variable of *alcohol screen result* was found to be largely different in the American Indian group when compared to the other groups (45.3% documented as present). Looking at *ethnicity*, non-Hispanic patients had a value for *alcohol screen result* 27.5% of the time compared to 21.4% of the time for Hispanic or Latino patients. Non-Hispanic patients had a *THC* value documented 26% of the time compared to 23.3% of the time in Hispanic or Latino patients. *Total GCS* was present in 93.8% of the time in the non-Hispanic group compared to 94.7% of the time for Hispanic or Latino group. This shows that data missing amongst these variables can be attributed to chance.

When considering the crosstabulation for *THC Combo*, or THC presence, it was found that patients who had a negative test for THC were more likely to have missing data for alcohol result when compared to those who tested positive. For those who tested negative, 55.8% had a value reported for *alcohol screen result* compared to 86.5% for those who tested positive. This aligns with the clinical scenario in that patients who had a blood sample drawn to test for substances had a higher chance of testing positive than those who did not get a blood sample drawn, as all substances are tested using the same sample and sample time. If a patient was having blood drawn to test for alcohol, they were also likely to be tested for other substances. The results were similar when looking at all the *positive for drugs* table. Patients who tested negative for all other substances were more likely to have missing data for *alcohol screen result* when compared to those who had a positive test. For those who tested negative, 53.8% of the time there was a value documented for alcohol compared to 83.7% of the time in the presence of a positive substance test. This supports the idea that data for *THC Combo* may be missing if *alcohol screen result* is

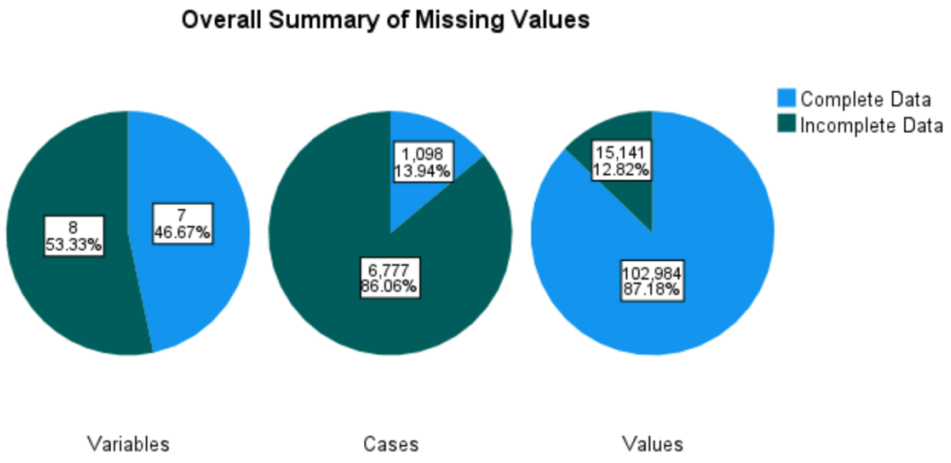
missing, which indicates that the missing values for *THC* may not be missing completely at random.

Little's MCAR Test. The results of Little's MCAR test appear in footnotes to each EM estimate table. The null hypothesis for Little's MCAR test is that the data are missing completely at random (MCAR). Data are MCAR when the pattern of missing values does not depend on the data values. Estimated mean correlations for Little's MCAR test were performed for the continuous variables of *age*, *alcohol screen result* and *total GCS*. The findings of the Little's MCAR test were as follows: Chi-Square = 750.736, DF = 9, Sig. = .000. The null hypothesis for Little's MCAR test is that data are missing completely at random (MCAR). Because the significance value is less than .05, it is concluded that the data are not missing completely at random.

Overall Patterns of Missingness. An overall summary of missing values analysis was performed. Three pie charts showing different aspects of the missing values in the data are displayed, as can be seen in Table 10. The *Variables* chart shows that 8 of the 15 analysis variables have at least one missing value on a case. The *Cases* chart shows that 6777 of the 7875 cases have at least one missing value on a variable. The *Values* chart shows that 15,141 of the 102,984 values (cases x variables) are missing overall in the dataset.

Table 10

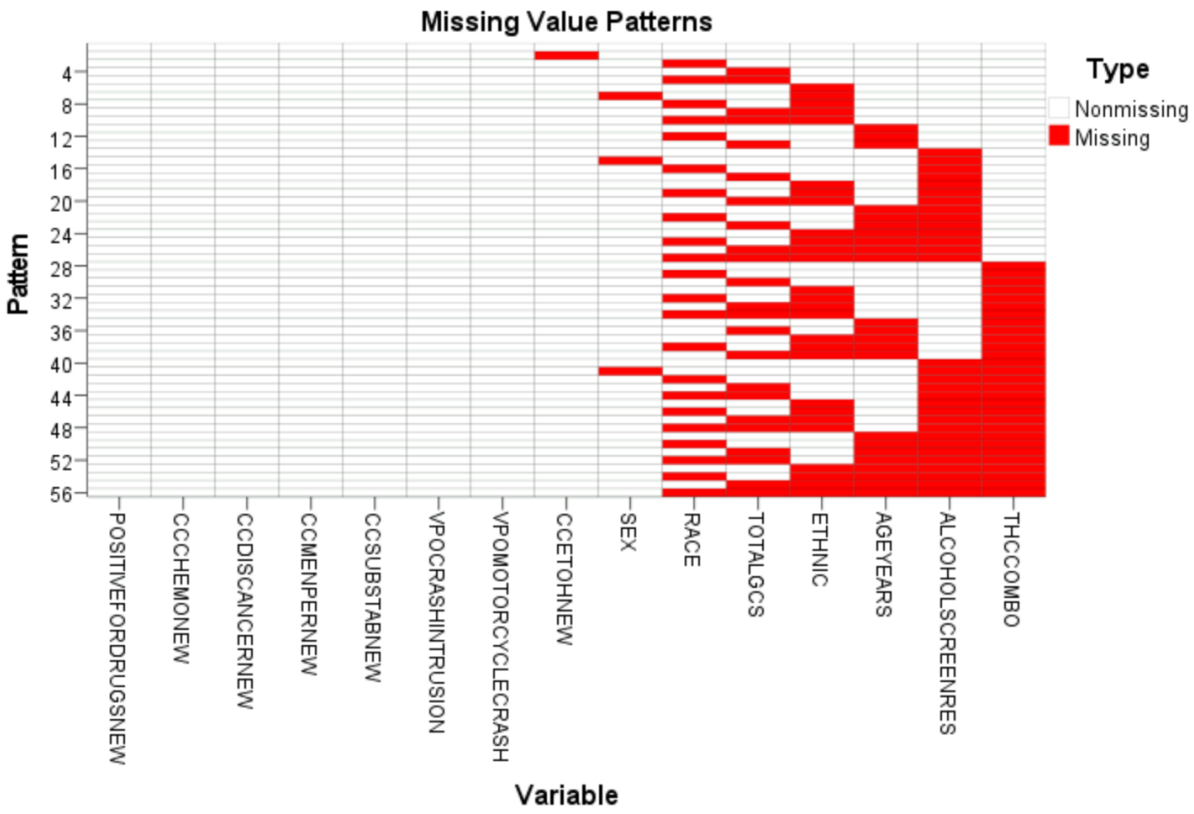
Overall Summary of Missing Values



Next, a missing value patterns box, composed of small red and white rectangle lines, displays value patterns for each of the analysis variables and suggests any patterns to the missing data. Each pattern corresponds to a group of cases with similar patterns of complete and incomplete data. The missing values patterns chart displays the patterns and analysis variables in a specific order to reveal monotonicity, which is a rigid pattern of missing data within the red lines. (IBM, 2012). Variables are placed from left to right in increasing order of missing values. Patterns are sorted by from right to left by non-missing values first then at the missing values found in the last variable, then by the second to last variable and so on to identify whether data are monotone. No patterns of missingness may be assumed if the red lines look randomly and evenly dispersed. If data are monotone, then all the non-missing cells and missing cells will be adjacent to each other as can be seen in the figure below. As can be seen in Table 11, this dataset has a tendency for monotonicity. (IBM, 2012).

Table 11

Missing Value Patterns

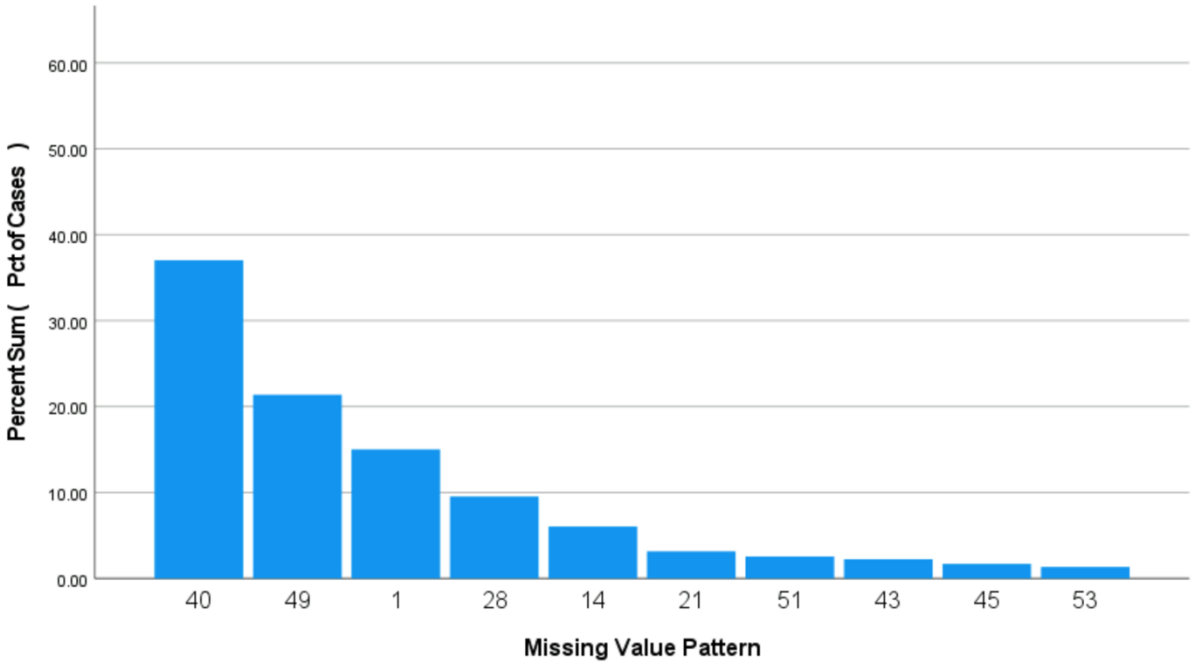


When patterns in SPSS are requested, a bar chart displaying the percentage of cases for each pattern is tabulated. The bar chart seen below in Table 13 shows that almost 40% of the cases in the dataset have Pattern 40, and the missing value patterns chart, as seen in Table 12, shows that this is the pattern for cases with a missing value on *alcohol screen result* and *THC Combo*. Pattern 49 represents cases with a missing value on *age, alcohol screen result and THC combo.* The bar chart shows that almost 15% of the cases in the dataset have Pattern 1, and the missing value patterns charts shows that this is the pattern for cases with no missing values. Pattern 28 represents cases with a missing value on *THC combo*. Pattern 14 represents cases with a missing value on *alcohol screen result*. The great majority of cases are represented by these four patterns. It is important to note that patterns 21, 51, 43, 45, and 53 are considerably smaller than the first

four patterns, and they are similar in size. This means that the patterns of missingness across the variables is somewhat consistent, and that no dominant pattern to the missingness is readily seen. Based on this extensive analysis, it was determined that variables total GCS, alcohol screen result and THC Combo are not missing completely at random.

Table 12

Bar Chart for Missing Value Pattern



Dealing with Missing Values. When missing values in each variable account for less than 5%, those values can be missing at random (the missing value does not depend upon other values) and listwise deletion can be performed relatively safely is appropriate to do. This holds true for all the variables except for *THC Combo, positive for drugs, alcohol screen result*, *age in years*, *ethnicity* and *total GCS*. These variables, three quantitative and three categorical, were found to have greater than 5% missing values. On observation of the missing value analysis, it was observed that most cases had these two variables as missing, perhaps suggesting a

relationship, or an effect. Furthermore, the Little's MCAR test revealed that missing data may not be missing completely at random. Deleting cases with missing values can reduce the statistical power of the analysis and result in biased outcomes and estimates. Therefore, the use of multiple imputation is appropriate for this dataset and this study. Another method in SPSS that can be utilized is the Replacing Missing Values method. The Linear Interpolation method will be utilized. The Linear Interpolation method is a simple statistical method used by SPSS which estimates the value of one variable from the value of another and using regression methods to find the line of best fit. Using the Replacing Missing Values method in this study will help solve the problem of bias and ensure that power is not decreased because a large majority of the sample size will be preserved.

It is important to consider the implications associated with imputing or replacing missing data. Multiple imputation or missing value replacement analyses will avoid bias only if enough variables predictive of missing values are included in the replacement method. If variables that may be predictive of the estimates are not included in the model, for example the effect of age on alcohol result, replacement computation will underestimate these associations and bias the final analysis. Therefore, it is preferrable to include as many predictive variables as possible in the model when either imputation or replacing missing value methods are utilized.

Rationale for Replacing Missing Values. Replacing missing values was utilized to minimize the many problems associated with missing data. The absence of data reduces statistical power and can also lead to bias in the estimation of parameters and analyses. Finally, missing data can diminish the representatives of the sample size and cases (Kang H., 2013). It is important to consider that though replacing or imputing data is a common approach to the problem of missing data, it still does not allow analyses of actual data that is provided by actual

participants, or in this case, data entered by abstractors and hospital registry systems. In gaining a larger sample size, and perhaps a more representative sample, confidence is lost that actual responses provided are those analyzed. It is important to note that methods used to account for missing data only provide researchers with the best estimated guess of what actual data may have been had it been documented in the first place. It is this ideology that influenced the decision to include some of the variables with missing data to be multiply imputed.

Replacing Missing Values Method. Replacing missing values is another form of multiple imputation that was selected for this study. Though multiple imputation process was utilized, it presented a complication in terms of the number of iterations and the subsequent analysis. Since the dependent variable, *total GCS*, was not selected for imputation/replacement, it was recommended and deemed appropriate to utilize the Replacing Missing Values function in SPSS to establish estimates for a select group of variables with missing data values. Replacing Missing Values method, a different form of imputation, allows the creation of new variables from existing ones by replacing them with estimates computed with a variety of methods. For this study, the Linear Interpolation method was used. This method utilizes the last valid value before the missing value and the first valid value after the missing value.

The variables selected for missing value replacement were *age* and *alcohol screen result*. The variable *age* was selected due to its effect on traumatic brain injury incidences as well as post TBI outcomes (Gardner, R et al., 2018). Additionally, the use of alcohol and other substances is prevalent in young adults with more than half of those who die from overdoses being younger than 50 years of age (Ritchie & Roser, 2018). The impact of age on TBI, substance abuse and outcomes could not be overlooked, and omitting this large percentage of cases will bias analysis results. The variable of alcohol screen result was also important to

replace because of the known impact and association alcohol abuse has on TBI incidence and outcomes. Alcohol and TBI are closely associated, with up to 50% of adults noted to drink more alcohol than recommended prior to their injury, and ultimately incurring worse outcomes (Bombardier & Turner, 2009; Corrigan et al., 2012). The variables of *total GCS*, *THC Combo* and *positive other drugs* were not included. *Total GCS (*494 missing values; 6.3%*)* is the dependent variable, and having estimates instead of actual data seemed conceptually and logically inappropriate. For being the main predictor variables, both *THC Combo* and *positive other drugs* were not included to ascertain a more accurate and true account of the effects they may have on TBI severity.

Final Data Set. The Replacing Missing Values method yielded 7872 entries for *age*, with only 3 missing cases. The mean for *age* in the new dataset with replaced values was 31.19 years with a standard deviation of 26.1 compared to 33.78 years with a standard deviation of 27.3 for the non-replaced dataset. The replacing missing values method yielded 7822 (53 missing cases) valid entries for *alcohol screen result*, compared to 2087 entries in the non-replaced dataset. In the new dataset, *alcohol screen result* had a mean of .03, a standard deviation of .0752, with a minimum value of .00 and a maximum value of .66.

The original dataset, with 7875 cases, was used for the missing value replacement method, because as mentioned previously, it is preferrable to include as many predictive variables as possible in the model so that the new replaced/imputed values are indeed best estimates. Once the dataset had the missing variables for *age* and *alcohol screen result* replaced, the dataset was then amended to only include participants greater than 16 years of age to meet the inclusion criteria. Once those cases were removed, the final dataset consisted of 4910 unique cases.

Data Analysis

Aim 1

Aim 1 set to explore the prevalence of marijuana exposure in patients with traumatic brain injury. Statistical analyses were conducted using SPSS (version 25) software. Descriptive statistics were used to describe the study population. As shown in Table 13, men accounted for 67% of all study participants. The mean age of study participants was almost 47 years of age. Sixty seven percent of the study population identified as white, and 81% of study participants identified as not Hispanic or Latino. Mean GCS score was 13.11, indicating a moderate TBI score. Almost 94% of the final study population had a documented GCS score. In a sample of 4910 unique cases, 304 (6.2%) values corresponded to a yes as having THC on board at the time of exposure. Table 13 delineates the descriptive statistics of the key variables.

Table 13

Descriptive Statistics of Key Variables

Variable	*N*	*%*	*M*	*SD*	Missing/Percent	Min.	Max.
Age	4910	-	46.78	20.852	-	16	89
Alcohol Screen Result	4887	99.5	0.0472	0.0903	23 (0.5)	0	0.66
Total GCS	4615	94	13.11	3.889	295 (6)	3	15
Sex	4908	99.9	-	-	2 (0.01)	-	-
Male	3291	67.1	-	-	-	-	-
Female	1617	32.9	-	-	-	-	-
Race	4780	97.4	-	-	130 (2.6)	-	-
Asian	107	2.2	-	-	-	-	-
Pacific Islander	16	0.3	-	-	-	-	-
American Indian	40	0.8	-	-	-	-	-
Black	814	16.6	-	-	-	-	-
White	3322	67.7	-	-	-	-	-
Other	473	9.6	-	-	-	-	-
Multi-racial	8	0.2	-	-	-	-	-
Ethnicity	4584	93.4	-	-	326 (6.6)	-	-
Not Hispanic or Latino	3997	81.4	-	-	-	-	-
Hispanic or Latino	587	12	-	-	-	-	-
THC	1663	33.9	-	-	3247 (66.1)	-	-
Tested Negative	1359	27.7	-	-	-	-	-
Tested Positive	304	6.2	-	-	-	-	-
Drugs	1662	33.9	-	-	3248 (66.2)	-	-
Tested Negative	1281	26.1	-	-	-	-	-
Tested Positive	381	7.8	-	-	-	-	-

Variable	*N*	*%*	*M*	*SD*	Missing/Percent	Min.	Max.
CC Chemo	4780	97.4	-	-	130 (2.6)	-	-
No Chemo	4769	97.2	-	-	-	-	-
Yes Chemo	11	0.2	-	-	-	-	-
Disseminated Cancer	4780	97.4	-	-	130 (2.6)	-	-
No Disseminated Cancer	4747	96.7	-	-	-	-	-
Yes Disseminated Cancer	33	0.7	-	-	-	-	-
Mental/Personality Disorder	4780	97.4	-	-	130 (2.6)	-	-
No Mental/Personality	4402	89.7	-	-	-	-	-
Yes Mental/Personality	378	7.7	-	-	-	-	-
Substance Abuse	4780	97.4	-	-	130 (2.6)	-	-
No Substance Abuse	4540	92.5	-	-	-	-	-
Yes Substance Abuse	240	4.9	-	-	-	-	-
Alcohol Abuse	4780	97.4	-	-	130 (2.6)	-	-
No Alcohol Abuse	4447	90.6	-	-	-	-	-
Yes Alcohol Abuse	333	6.8	-	-	-	-	-
MOI Crash	4910	100	-	-	-	-	-
No Crash	4888	99.6	-	-	-	-	-
Yes Crash	22	0.4	-	-	-	-	-
MOI Motorcycle	4910	100	-	-	-	-	-
No Motorcycle	4894	99.7	-	-	-	-	-
Yes Motorcycle	16	0.3	-	-	-	-	-

Aim 2

Aim 2A Independent *t*-test. The first objective for aim 2 is to compare the group with THC on board and the group without THC on *total GCS* and TBI severity. An independent-samples t-test was conducted to compare total GCS in the group of participants who tested negative for THC (assigned a code of 0) and those who tested positive (assigned a code of 1). The dataset does meet the assumptions required for an independent-samples t-test: 1. the dependent variable, *total GCS*, is continuous; the independent variable, *THC Combo*, is categorical; cases have values on both the dependent and independent variable; there is an independence of observations and participants in the first group are not in the second; the dataset includes a random sample; and the dataset includes a large sample size and therefore address assumption of normality. The null hypothesis (H_0) and alternative hypothesis (H_1) is expressed below, where μ_1 and μ_2 are the population means for group 1 and group 2 respectively. Group 0 tested negative for THC and group 1 tested positive:

H_0: $\mu_{\text{negative-THC}} = \mu_{\text{positive-THC}}$ (the two population mean values are equal)

H_0: $\mu_{\text{negative-THC}} \neq \mu_{\text{positive-THC}}$ (the two population means values are not equal)

Group statistics revealed 1308 participants who tested negative compared to compared to 297 participants who tested positive. Mean total GCS scores for individuals who tested negative was 12.37 (*SD* 4.405) compared to 11.73 (*SD* = 4.736) for those who tested positive. Levene's Test for Equality of Variances showed an F = 11.177 and a $p < .001$. Therefore, the null of Levene's test is rejected to conclude that the variance in the GCS score of participants of tested positive was significantly different than that of those who tested negative. As a result, the equal variances not assumed row for the *t* test results was observed and revealed that there was a statistically

significant difference in mean GCS scores between participants who tested positive for THC and those who did not ($t_{420.030} = 2.129$, $p < .034$).

Aim 2B Group Characteristics. Based on toxicology test results, 1359 patients were in the *No THC* group and 304 patients in the *THC* group. Summary statistics of all patient characteristics by group are shown in Table 14. The *THC* group had a significantly higher number of males than the *No THC* group (OR = 0.56 [95% CI: 0.411 to .763], $p < .001$). The *No THC* group was significantly older than the *THC* group ($M = 47.14$, $SD = 14.78$, $p < .001$). There was no difference in *ethnicity* between any of the two groups $X^2(1, N = 1516) = .001$, $p = .974$; [95% CI: .691 to 1.464]). The two groups were statistically significant when compared with *GCS scores* as an outcome. The mean *GCS score* for the *No THC* group was 12.37 whereas the mean *GCS score* for the *THC* group was 11.73. The *THC* group had lower *GCS scores* indicating a worsened injury when compared to the *No THC* group ($t = 2.129$, $p = .034$). The mean blood *alcohol level* for the *No THC* group was .057 whereas the mean blood *alcohol level* for the *THC* group was .064; a slightly higher blood *alcohol level*, but not a statistically significant difference ($t = -1.119$, $p = .263$). There were also no significant differences between the two groups in *motor vehicle collision* mechanisms of injury (OR = 1.279 [95% CI: 0.264 to 6.188], $p = .759$). Similarly, there was no statistical difference between the two groups in *motorcycle collision* mechanisms of injury, despite a p value score less than .05 (OR = 5.474 [95% CI: 1.143 to 12.438], $p < .001$). Because the confidence interval is greater than 1 and has a wider range, it is then insufficient evidence to conclude that there was a statistically significant difference between the two groups of *THC* and *No THC*. There was a statistically significant difference in participants' *history of cancer* in the *THC* group $X^2(2, N = 1630) = 5.24$, $p = .073$. The *THC*

group also had a significant difference in participants' *history of substance abuse* when compared to the No THC group $X^2(2, N = 1621) = 64.763, p < .001$.

Table 14

Group Statistics for THC Positive and THC Negative

Characteristic	No THC (n=1359)	Mean	THC (n=304)	Mean	Levene's Test for F	Sig.	t	Sig. (2-tailed)	Chi-Square	df	Sig.	OR	95% Confidence Interval Lower	Upper
Sex									13.792	1	< .001	0.56	0.411	0.763
Male	955		246											
Female	402		58											
Age	1359	47.14 ± 20.33	304	34.79 ± 14.78	61.816	< .001	12.205	< .001					10.356	14.329
Race*									18.038	6	< .006			
Asian	39		3											
PI	8		1											
AI	12		7											
Black	249		**74**											
White	859		191											
Other	148		20											
Mult-racial	3		0											
Ethnicity									0.001	1	0.974	1.006	0.691	1.464
Not Hispanic	1062		251											
Hispanic	164		39											
GCS 3-15	1308	12.37 ± 4.40	297	11.73 ± 4.736	11.177	<.001	2.129	0.034					0.049	1.231
GCS ≤ 8	258		76											
GCS 9-12	144		8											
GCS ≥ 13	978		205											
Alcohol Screen	1356	0.057 ± .103	304	0.064 ± .108	0.879	0.349	-1.119	0.263					-0.02044	0.00559
Positive for Drugs*									91.593	2	< .001			
Tested Negative	1110		171											
Tested Positive	248		133											
CC Chemo									3.49	2	0.175			
No Comorbidity	1327		292											
Yes Comorbidity	2		0											
CC Cancer									5.24	2	0.073			
No Comorbidity	1319		292											
Yes Comorbidity	19		0											
CC Men/Per									3.275	2	0.194			
No Comorbidity	1299		31											
Yes Comorbidity	129		12											
CC Substance									64.763	2	< .001			
No Comorbidity	1235		227											
Yes Comorbidity	94		65											
CC Etoh									3.496	2	0.174			
No Comorbidity	1192		260											
Yes Comorbidity	137		32											
MV Collision									0.094	1	0.759	1.279	0.264	6.188
No	1352		302											
Yes			2											
MC Collision									5.474	1	0.019	3.771	1.143	12.438
No	1353		299											
Yes	6		5											

* See comparisions of colum proportions

To determine the relative ordering of categories of the categorical variables of *race* and *presence of other drugs*, a comparison of column proportions test was used. The column proportions test looks at each of the different rows of the race and presence of other drugs variables and compares pairs of columns testing them to determine whether the proportion of data in one column is significantly different from the proportion in the other. This test was

utilized because a chi-square test could not be calculated for multiple levels of categories within each selected variable. Tables 15 and 16 display the column proportions for the variables of *race* and *presence of other drugs*.

Table 15

Comparisons of Column Proportions for Race

		THC Combo		
		Tested Negative (A)	Tested Positive (B)	Missing (C)
Race	Asian			.[a,b]
	PI			.[a,b]
	AI			.[a,b]
	Black		A	.[a,b]
	White		A	.[a,b]
	Other	B		.[a,b]
	Multi-Racial		.[b]	.[a,b]

For *American Indians* and *Black* participants, the A key appears in the *THC* positive column. This indicates that the proportion of *American Indians* and *Black* participants who tested positive for *THC* is greater than the proportion of *Asian*, *Pacific Islanders*, *White*, *Other* and *Multi-Racial* participants. Additionally, the proportion of participants who tested negative is greater in the *other* race category when compared to all other groups. It is important to note that the *missing column* is marked with a ".", which indicates that no comparisons can be made using that column for the different categories of *race*. To reiterate, there was 2.6% of the data missing in the *race* variable.

Table 16

Comparisons of Column Proportions for Other Drugs

		THC Combo		
		Tested Negative (A)	Tested Positive (B)	Missing (C)
Positive for other drugs	Missing		.[a]	.[a,b]
	Tested Negative	B		.[a,b]
	Tested Positive		A	.[a,b]

The proportion of participants who tested negative for THC and were also negative for other drugs was greater than the proportion of participants who tested positive for THC. Alternatively, the proportion of participants who tested positive for THC and tested positive for other drugs was greater than the proportion of participants who tested negative for THC. For the variable of presence of other drugs, 66% of the data was missing. This is important to consider when reporting results of column proportions, as no comparisons can be made between the groups in the context of missing data.

Aim 3

Aim 3A One-Way Anova. Aim 3A was to determine the relationship between presence of THC and effects on GCS scores. The analysis for the one-way ANOVA examining the unadjusted relationship between the presence of THC and its effect on GCS score (3-15) was analyzed. Pairwise deletion was utilized in the analysis. Pairwise deletion allows the inclusion of more data as it does not prevent the statistical analysis from using cases with a missing value. Additionally, pairwise deletion was utilized because the probability that any of the predictor values are missing cannot depend on the dependent variable, *total GCS*, which in this study, the probability that alcohol is missing does not depend on the GCS score. To recap, the variable

alcohol screen result had 0.5% missing values (23/4910) while the variable *total GCS* had 6% of its values missing (295/4910), Therefore, pairwise deletion was appropriate in this analysis.

The Model Summary table provides the *R* and R^2 values. The *R* value represents the simple correlation and is .056 for the new multiple imputation dataset. The R^2, which indicates how much of the variance in the dependent variable (*total GCS*) can be attributed to the independent variable (*THC presence*). In this case, *3*% of the variation in *total GCS* can be explained by the presence of THC. Next, the ANOVA table, which reveals how well the regression equation predicts the dependent variable of total GCS, is displayed. When the data set is analyzed, it was found that the regression model was significant, F (1,1603)=4.964, p = .026. Next, the effect of THC (b = -.569, p = .026) is statistically significant and its coefficient is negative indicating that for everyone unit increase in *THC presence*, total GCS decreases by .569.

Table 17

One-Way ANOVA Table Examining THC Presence and Total GCS

	Sum of Squares	df	Mean Square	F	Sig.
Regression	77.503	1	77.503	4.964	0.026
Residual	25029.646	1603	15.614		
Total	25107.148	1604			

a Dependent Variable: TOTALGCS
b Predictors: (Constant): THCCOMBO

Aim 3B Correlations of Covariates. A Pearson correlation coefficient was computed to assess the relationship between total GCS, age, and alcohol screen results. Table 20 displays the correlations output which measure the strength and direction of the linear relationship between the three continuous variables in the model. The variables included are *total GCS*, *age*, and *alcohol screen result*. The correlation coefficient ranges from -1 to +1, with -1 indicating a

negative correlation and +1 a positive correction. A 0 value indicates no correlation at all. There was a positive correlation between *age* and *GCS scores*, $r = .076$, $N = 4615$, and the relationship was statistically significant $p = .000$. This means that increases in age were correlated with an increase in total GCS scores, though the correlation is small. Conversely, there was a small, negative correlation between *alcohol screen result* and *GCS scores*, $r = -.087$, $N = 4592$, and that relationship was also statistically significant $p = <.001$. This indicates that increases in alcohol levels were correlated with a decrease in GCS scores, indicating a worse neurological status. Finally, there was a small, negative correlation between *age* and *alcohol result*, $r = -.038$, $N = 4887$, and the relationship was statistically significant $p = .004$. An increase in alcohol level was correlated with a decrease in age, or younger patients.

Table 18

Correlations for Total GCS, Age and Alcohol Result

		TotalGCS	AgeYears	AlcoholResult
Pearson Correlation	TotalGCS	1	0.076	-0.087
	AgeYears	0.076	1	-0.038
	AlcoholResult	-0.087	-0.038	1
		-0.087		
Sig. (1-tailed)	TotalGCS	.	<.001	<.001
	AgeYears	0	.	0.004
	AlcoholResult	0	0.004	.
N	TotalGCS	4615	4615	4592
	AgeYears	4615	4910	4887
	AlcoholResult	4592	4887	4887

Aim 3C Multicollinearity Analysis. This section will discuss the effect the predictor variables have on *total GCS* as an overall group, and individually. Before the analysis was run, a dummy variable for the variable *Race* was used to represent the seven subgroups within the study sample. This was done so that the regression analysis could be performed while representing multiple groups. Next, to assess collinearity, a linear regression analysis utilizing

pairwise deletion was performed, and included the following predictor variables: *sex*, *age in years* (replaced/imputed), *alcohol screen result* (replaced/imputed), *ethnicity*, *THC Combo*, *positive for drugs*, *CC Substance abuse*, and the dummy code for *Race* with *White* as the reference value. The variable *White* was used as it was the largest represented race category.

Descriptive statistics revealed the following means for *total GCS* (M = 13.11), *age in years* (M = 46.78) and *alcohol screen result* (M = .0472). The Model Summary for this analysis showed analysis revealed a R value of .370 and a R^2 of .137, which indicates that 13.7% of the variation in *total GCS* can be explained by the model overall; it does not account for the variance effect by individual predictors. The overall regression model was significant, F (8,1507) = 29.827, $p < .001$, $R^2 = .137$.

Table 19 describes the coefficients values for each of the predictor variables. The coefficients table was evaluated at an alpha value of .05.

Table 19

Table of Coefficients and Multicollinearity

	Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B		Collinearity Statistics	
	B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound	Tolerance	VIF
(Constant)	11.78	0.321		36.743	<.001	11.153	12.411		
LINT (AGEYEARS)	0.007	0.005	0.038	1.538	0.124	-0.002	0.017	0.889	1.125
LINT (ALCOHOLSCREERES)	-3.906	1.074	-0.089	-3.638	<.001	-6.013	-1.8	0.926	1.08
SEXRECODED	0.874	0.205	0.104	4.254	<.001	0.471	1.276	0.936	1.068
ETHNICRECODED	0.486	0.289	0.041	1.681	0.093	-0.081	1.053	0.935	1.07
THCCOMBO	0.195	0.264	0.019	0.737	0.461	-0.323	0.713	0.836	1.196
POSITIVEFORDRUGSNEW	-0.014	0.002	-0.167	-6.853	<.001	-0.018	-0.01	0.938	1.066
CCDISCANCERNEW	-1.113	0.545	-4.473	-2.041	0.041	-2.183	-0.043	0	8620.529
CCMENPERNEW	-0.829	0.35	-3.333	-2.368	0.018	-1.515	-0.142	0	3555.953
CCSUBSTANEW	-0.549	0.452	-2.208	-1.214	0.225	-1.437	0.338	0	5935.267
CCETOHNEW	2.575	0.401	10.318	6.429	<.001	1.79	3.361	0	4622.642
VPOCRASHINTRUSION	-1.454	1.399	-0.025	-1.039	0.299	-4.199	1.29	0.998	1.002
VPOMOTORCYCLECRASH	-2.164	1.646	-0.031	-1.315	0.189	-5.392	1.065	0.992	1.008
WHITEDUMCODE	-0.036	0.212	-0.004	-0.171	0.864	-0.452	0.379	0.918	1.09

a. Dependent Variable: TOTALGCS

The Coefficients table also allows the testing of the assumption that there is no multicollinearity in the data. The *VIF* and *Tolerance* statistics assess this assumption, and to meet this assumption,

the *VIF* scores need to below 10 and the *Tolerance* scores above 0.2. Tolerance is the proportion of variance in any single independent variable not explained by the other independent variables. Immediately, it can be noted that the predictor variables for comorbid conditions including *disseminated cancer*, *mental/personality disorder*, *substance abuse disorder*, and *alcohol abuse disorder* all had *Tolerance* scores of zero, and *VIF* scores ranging from 3355 to 8620. One comorbid condition, *chemotherapy*, was excluded from the overall analysis. This is because this variable can be perfectly predicted by one or more other variables, in this case the presence of *disseminated cancer*. Only one of these two variables can be used as a predictor in the model. Furthermore, it can be noted that there is perfect collinearity among all the comorbid conditions. Hence, the *Tolerance* scores are all zero, and the *VIF* scores are all greater than 10. It is for this reason that these variables cannot be considered when interpreting the results. Tests of collinearity indicated that multicollinearity was not a concern regarding the remaining variables (*Sex*, *Tolerance* = .936, *VIF* = 1.068; *Age*, *Tolerance* = .889, *VIF* = 1.125; *Alcohol screen result*, *Tolerance* = .926, *VIF* = 1.080; *Ethnicity*, *Tolerance* = .935, *VIF* = 1.07; *THC Combo*, *Tolerance* = .836, *VIF* = 1.196; *Positive for drugs*, *Tolerance* = .938, *VIF* = 1.066; *White* (dummy code for *race*), *Tolerance* = .918, *VIF* = 1.09).

Because even one variable that has evidence of multicollinearity affects the entire model, it was determined that the model be re-run using only one of the comorbid conditions variable. This was done to help eliminate multicollinearity and provide a more stable model and stronger regression analysis. The variable selected for inclusion was *history of substance abuse.* This variable was selected as it is closely related to the study aims which involves marijuana. Since marijuana is commonly used in conjunction with other drugs, it made logical sense to include the *history of substance abuse* into the regression analysis.

When the four variable of comorbid conditions were excluded, multicollinearity was then eliminated. Table 20 delineates the new model, including coefficients and collinearity statistics.

Table 20

Table of Coefficients and Multicollinearity Revised

	Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B		Collinearity Statistics	
	B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound	Tolerance	VIF
(Constant)	11.947	0.322		37.145	<.001	11.316	12.578		
SEX	0.673	0.206	0.08	3.273	0.001	0.27	1.076	0.96	1.041
AGE	0.008	0.005	0.045	1.76	0.079	-0.001	0.018	0.892	1.121
WHITE DUMMY CODE	0.047	0.214	0.005	0.219	0.827	-0.372	0.466	0.927	1.079
ETHNICITY	0.49	0.293	0.041	1.673	0.095	-0.084	1.065	0.936	1.068
ALCOHOL SCREEN	-2.518	1.058	-0.058	-2.381	0.017	-4.593	-0.443	0.982	1.019
THC	-0.172	0.253	-0.017	-0.678	0.498	-0.668	0.325	0.935	1.069
OTHER DRUGS	-0.012	0.002	-0.145	-5.981	<.001	-0.016	-0.008	0.98	1.021
HISTORY OF SUBSTANCE ABUSE	0.075	0.006	0.303	12.616	<.001	0.064	0.087	0.995	1.005

a. Dependent Variable: TOTALGCS

Tests of collinearity indicated that multicollinearity was not a concern regarding the new model with the following variables (*Sex*, *Tolerance* = .96, *VIF* = 1.041; *Age*, *Tolerance* = .892, *VIF* = 1.121; *Alcohol screen*, *Tolerance* = .982, *VIF* = 1.019; *Ethnicity*, *Tolerance* = .936, *VIF* = 1.068; *THC*, *Tolerance* = .935, *VIF* = 1.069; *Other drugs*, *Tolerance* = .98, *VIF* = 1.021; *White* (*dummy code for race*), *Tolerance* = .927, *VIF* = 1.079; *History of substance abuse*, *Tolerance* = .995, *VIF* = 1.005).

Aim 3D Regression Analysis. A multiple regression was carried out to investigate whether the presence of THC influences total GCS and TBI severity adjusting for other variables. Table 19 depicts the findings of the linear regression analysis. In the adjusted regression, the presence of THC was associated with a lower GCS score, but the finding was not statistically significant (*B* = -.172, *p* = .498). GCS scores decreased by .172 units, indicating a worsened GCS score and a more severe TBI. In terms of covariates, when the unstandardized *B* coefficients are examined, it can be determined that there was an inverse relationship between the variables of *alcohol screen result*, *presence of another drug*, and *GCS scores.* For everyone

unit increase in *alcohol screen result* decreased GCS scores by 2.518 units, a statistically significant result (p = .017). The inverse relationship is similar for patients who tested *positive for other drug,* though smaller. For every unit increase in *other drugs*, there was a decrease of .012 units in *total GCS,* also a statistically significant result (p = <.001).

Conversely, there was a small, positive relationship between *age* and *GCS scores*. For everyone unit increase in age, there was a .008 increase in total GCS, though not a statistically significant finding (p = .079). *Sex* was also associated with a positive relationship with a much larger relationship. For every one-unit increase, with males coded as 0 and females as 1, there is a .673 increase in GCS. This means that females have higher GCS scores than males when controlling for other variables, a statistically significant finding (p = .001). A positive correlation was found between having a *history of substance abuse* and *GCS scores*. For every unit increase in *history of substance abuse,* meaning a diagnosis of *substance abuse*, *GCS scores* increased by .075, a statistically significant finding (p = <.001). Finally, for everyone unit increase for the dummy variable *white*, *total GCS* increased by .047 units more than everyone else in the study sample, however, the finding was not statistically significant (p = .827).

The results of the regression indicated that the model explained 13.7% of the variance and that the model was a significant predictor of total GCS scores, $F(8, 1507) = 29.827$, $p < .001$. While *sex* (B = .673, p = .001), *alcohol screen result* (B = -2.518, p = .017), the *presence of other drugs* (B = -.012, p < .001), and *history of substance abuse* (B = .075, p = .< .001) contributed significantly to the model, the other predictor variables did not. Those variables are: *age* (B = .008, p = .079), *ethnicity* (B = .49, p = .095), *presence of THC* (B = -.172, p = .498), and *white* (B = .047, p = .827).

Aim 3E Mediation Analysis. The third objective for aim 3 is to determine the relationship between marijuana exposure at the time of injury and TBI severity, while examining any mediating effects by mechanism of injury (*motor vehicle crash intrusion*). The analysis showed only two participants had a motor vehicle crash, hence, it is not appropriate to perform a mediation analysis. I, however, did so and documented the process for my own learning purposes.

Because the mediator variable was a dichotomous variable, the Barron and Kenny (1986) method was used. Following step 1 of Barron and Kenny's method, the relationship between the predictor variable (*X*; *THC Combo*) and the dependent variable (*Y*; *total GCS*) was tested for significance. Step 2 of Barron and Kenny's method would be then used to test the relationship between *X* (*THC Combo*) and the mediator variable (*M*; *Motor vehicle crash intrusion*) for significance. If a significant relationship was found, then step 3 was tested, and *Y* (*total GCS*) was regressed on both *X* (*THC Combo*) and M (*Motor vehicle crash intrusion*).
The variable *motor vehicle crash intrusion* was examined to see if it mediated the relationship between *THC* presence and *total GCS*; hence TBI severity.

First, *THC Combo* (*X; predictor variable*) was regressed on *total GCS* (*Y; dependent variable*). The relationship between *THC* presence and *GCS score* was statistically significant (*B* = -.640, *SE* = .287, *t*(1603) = -2.228, *p* = .026), therefore, it is recommended to continue with mediation analysis for motor vehicle crashes. *THC Combo (X; predictor variable)* was then regressed on *motor vehicle crash intrusion (M; mediator variable)*. The relationship between *motor vehicle crash intrusion* and *THC Combo* was not significant (*B* = .001, *SE* = .005, *t*(1661) = .307, *p* = .759). However, when *THC Combo (X; predictor variable)* was regressed on *motorcycle crash collision (M; mediator variable)*, a significant relationship was observed (*B* =

.012, *SE* = .005, *t* (1661) = 2.342, *p* = .019). Therefore, an analysis of *motorcycle crash collision* ensued.

Motorcycle crash collision (M; mediator variable) was then regressed on *GCS scores (Y; dependent variable)* and the relationship was found to be statistically significant (*B* = -2.873, *SE* = .990, *t* (4613) = .-2.902, *p* = .004. The final step involved a regression analysis with *THC* presence and *motorcycle crash collision* and their effect on *GCS scores*. When analyzed, the model was found to be significant, with presence of THC and *motorcycle crash collision* having a statistically significant relationship/effect on *GCS scores*, hence TBI severity (*B* = .001, *SE* = .005, *t*(1661) = .307, *p* = .759). In this last step, it was found that the effect of *motorcycle crash collisions* remains significant after controlling for *THC* presence, which suggests the presence of partial mediation.

CHAPTER 6: DISCUSSION

Discussion

Aim 1

The first aim of this study was to identify the prevalence of THC in a purposive sample of TBI patients. In this study, it was found that 27.7% of study participants tested negative for THC, and 6.2% of study participants had tested positive for THC on presentation to the emergency department. An overwhelmingly large percentage of the data was attributed as missing, 66% to be exact. This large percentage of missing data makes it difficult to have confidence in the 6% prevalence rate found in this study. National surveys on drug use and health have documented an increase in individual daily marijuana use over the last 5 years, with almost 22 million users each month in the United States (CDC, 2018). Federally, marijuana use remains illegal in the United States, however, in 2017, the year corresponding to the data of this study, 29 states had legalized marijuana for medical use, and 8 states for recreational use. A recent study has found that marijuana use tends to be higher in states that have legalized its use compared to marijuana use in the United States overall (Dills et al., 2021). As a result, it is difficult to have confidence in the low prevalence rate found in this study.

Another important consideration to make regarding the large percentage of missing data is the scarcity of studies investigating marijuana use and prevalence in TBI patients. As noted earlier in the literature review, only one study, by Nguyen et al. (2014), investigated the effects of THC presence on mortality in patients who had sustained a TBI, and they reported a prevalence rate of 18.4%. However, Nguyen's et al. (2014) study involved a 3-year retrospective review of data obtained from a local hospital-based database, which can perhaps help explain their higher prevalence rate. The availability of a larger sample size because of 3 years' worth of

data may have contributed to that study's higher prevalence rates. A recent publication has already noted areas of improvement necessary for the NTDB to improve data quality and completeness (Phillips et al., 2008). It is important to note that the dataset used for this study reflects only one year worth of data, from 2017. At the start of this research study, the last dataset available for use was from 2017; datasets from 2018 and onward had not yet been released. Therefore, establishing previous prevalence rates for comparison, from the NTDB, could not be calculated because the presence of THC was never abstracted nor documented in earlier NTDB databases established before 2017.

Finally, it is imperative to consider what happens at the bedside, or the clinical setting, when trying to understand why there is a large percentage of missing data when it comes to the presence of THC. When it comes to the care of the trauma patient, it is a common expectation amongst trauma centers, that a urine drug screen would be completed on every trauma patient presenting the emergency department. Despite this, drug screens are often either not obtained, not resulted, or not documented by the clinical team. At times, clinicians may simply forget to draw a screen and send it to the lab. This commonly occurs in patients who do not receive a foley catheter, a practice that is now encouraged in hospitals. As a result, patients may take a while to urinate, often doing so in the absence of the trauma nurse, or later in another unit or when under the care of a non-trauma nurse who then simply forgets to collect the sample. At times, the sample may be collected, but the result was never documented in the medical record. All these clinical factors can also contribute to the missing data by simply not including it in the medical record, and ultimately not making it into the trauma registry itself.

Aim 2

When examining the differences between the group of participants with THC and those without and the influence on TBI severity, it was noted the group of participants who tested positive for THC had worsened GCS scores compared to those who tested negative for THC on presentation to the emergency department. The findings were significant, indicating that individuals who were positive for THC had a worsened neurological status as evidenced by lower GCS scores than those who tested negative. This finding is different than findings reported in the study by Nguyen et al. (2014), which examined the relationship between the presence of THC and mortality after TBI. Their study only focused on mortality after TBI and not TBI severity.

Based on toxicology test results, participants who tested positive for THC had a significantly higher number of males. Additionally, participants in the group that tested negative for THC were significantly older than participants who tested positive. This is supported by the literature, which indicates that men are more likely than women to use marijuana, as well as almost all other types of drugs (National Institute on Drug Abuse, 2021). Individuals 18-29 years of age were the largest group of marijuana uses in the US in 2019 (Statista, 2020). Marijuana use dropped among older age groups, with seniors the least likely to use marijuana (Statista, 2020). No differences were noted in Non-Hispanic versus Hispanic groups regarding marijuana use. Marijuana use was higher in the American Indian and Black participants when compared to all other race groups. Participants who identified as 'other' had a greater proportion of testing negative compared to all other race groups. Marijuana use disorder was greatest among African Americans compared to other race/ethnicities (Pacek et al., 2012). Marijuana policies are rapidly evolving in the United States, however, previous marijuana laws disproportionately targeted communities of color before legalization, and many policy makers argue that new

policies are not being developed with the input of minority stakeholders. Biomedical research has also marginalized and underrepresented communities of color. There is an obligation on the part of researchers, especially in the context of trauma and marijuana use, to actively work toward improving equity in marijuana related research.

The mean blood alcohol level for participants in the group that tested positive for marijuana was higher when compared to the group that tested negative. Though the difference was not statistically significant, it corroborates finding from the literature, that marijuana is the most used drug among individuals who drink. A study by Subbaraman and Kerr (2015) found that individuals who use both marijuana and alcohol tend to use them at the same time, and that the odds of drunk driving, social consequences and harms to self were doubled.

Participants who had a history or presence of cancer were more likely to test positive for marijuana compared to those who did not have a history or presence of cancer. The difference was statistically significant. Studies examining the use of marijuana for the treatment and management of symptoms medical conditions such as cancer is growing rapidly. There is evidence suggesting that cannabis for medical use reduces chronic and neuropathic pain in cancer patients (Blake et al., 2017). These studies support the finding in this study that a larger proportion of patients who tested positive for marijuana had cancer documented as a comorbidity.

Similarly, participants who had a substance abuse as a history or comorbid condition documented were more likely to test positive for THC when compared to those who did not have substance abuse as a comorbid condition. This finding too is supported in the literature, as marijuana use has been associated with concurrent use of other drugs (Tzilos et al., 2014). An important consideration needs to be made in the context of this finding; for the variable of

presence of other drugs, 66% of the data was missing. Since there is a large percentage of missing data, results should be cautiously interpreted and not assumed to be valid at face value in the context of such a large percentage of missing data. Lastly, no differences were found between the two groups of participants who tested positive and those who tested negative for THC when looking at likelihood of being involved in a motor vehicle of motorcycle collision.

Aim 3

Aim 3A. The relationship between the presence of THC and TBI severity was examined using a one-way ANOVA. This unadjusted analysis revealed a significant relationship between presence of THC and TBI severity, where the presence of THC was associated with a decrease in GCS. To reiterate, lower GCS scores indicates a potentially worse TBI, in the absence of severe intoxication or heavy sedation.

Aim 3B. This study indicated a significant relationship between GCS scores, sex, alcohol results, and history of substance abuse. There is a small positive correlation between age and GCS scores which suggest that increases in age were correlated with an increase in GCS scores. Conversely, there was an inverse relationship between alcohol screen results and GCS scores, where higher blood alcohol screen results were significantly associated with lower GCS scores, and ultimately, more serious TBIs. Lastly, age and alcohol were also correlated significantly, with higher alcohol levels in younger patients. These findings are supported by research studies that investigate the relationship between alcohol, age and TBI severity. In a recent study by Leijdesdorff et al. (2020), it was found that TBI patients with high blood alcohol levels were predominantly male and were younger. Furthermore, TBI patients with positive blood alcohol levels were found to have higher levels of disability and significantly poorer cognitive outcomes on discharge (Mathias & Osborn, 2016).

Aim 3C. Tests of collinearity indicated that multicollinearity was not a concern regarding the included variables

Aim 3D. While patients with a positive THC test had significantly lower GCS scores on admission when compared to patients who did not have THC, or were not known to have THC on admission to the ED. Once other variables, including age, presence of alcohol on admission, sex, presence of other drugs and comorbidities were considered, findings indicated that the presence of THC was indeed associated with lower GCS scores, hence worsened TBI severity, however, the findings were not statistically significant. Age, race, ethnicity, motor vehicle collisions, and motorcycle collisions were also not shown to be independent predictors of TBI severity. Conversely, sex, presence of alcohol on admission, presence of other drugs, and a history of substance abuse were identified as independent predictors of TBI severity.

Being female was associated with higher GCS scores indicating a less severe TBI. Similar to findings in previous studies examining TBI and sex, 67% of the study sample were male, while 32.9% of the sample were female. Gender differences in TBI incidence have been well documented, with men more likely to engage in injury-prone work or high-risk dangerous behavior (Hyder et al., 2007; de Guise et al., 2014). Additionally, women are less likely to be involved in a physical altercation than men (de Guise et al., 2014). Furthermore, gender differences, can influence clinical outcomes between men and women. Research studies have proposed that female steroid hormones may exert some neuroprotective effects through anti-inflammatory and antioxidant processes and may therefore explain why women tend to have better cognitive and functional outcomes after a TBI when compared to men (Berry et al., 2009).

As expected, this study showed that the presence of alcohol and drugs at the time of injury were independent predictors of lower GCS scores, or otherwise a moderate or more severe

TBI. The TBI literature does provide evidence of a close relationship between substance abuse disorder and TBI (Niemeier et al., 2016). Research has identified alcohol use as a common element in individuals with a brain injury. Large percentages of patients who have sustained a TBI have a history of alcohol abuse and drug use, up to 79% and 33% respectively (Taylor et al., 2003). In another study by Andelic et al. (2010) found that 35% of TBI patients were under the influence of alcohol. In this study there was a large percentage of alcohol levels missing, therefore, data was imputed. If in the original data set values were consistently measured and recorded, then findings regarding alcohol presence at presentation would possibly be much higher. Nevertheless, with the imputed values only 23 (0.5%) unique cases did not have an alcohol result. This too, may bias the finding, but like other study findings, this study's finding showed that when alcohol was present at the time of injury participants had a lower GCS score, hence a more severe TBI indicating a worsened neurological status at presentation.

Likewise, patients who were positive for at least one substance/drug were also found to have lower GCS scores and worsened TBI severity. Similar to findings in studies involving alcohol and brain injury, substance abuse was associated with poorer neuropsychological and functional outcomes (Andelic et al., 2010; Niemeier et al., 2016). Literature reviews also support this finding, with findings indicating that almost 40% of TBI patients had a positive toxicology screen, or had reported using drugs, with marijuana use accounting for more than half of the drug use (Bombardier et al., 2002). Similar to the large percentage of missing data for *alcohol screen*, the variable *presence of other drugs* also had a large percentage of missing data (66%). This is important to consider, as a large percentage of missing data may cause bias. Yet, in this study, even with the large percentage of missing data, the presence of other drugs was found to

have a negative influence on TBI severity as indicated by lower GCS scores compared to those who did not have other drugs present on admission.

It is important to consider that both alcohol and drug use at the time of injury can confound GCS assessment in trauma patients. Although findings from this study corroborate findings from TBI literature examining substance use, it may be judicious to acquire GCS scores after any intoxicating substances have worn off, perhaps hours or even up to a few days post injury. The GCS score is often assessed numerous times in a trauma patient's hospital stay, however, the NTDB data set does not include other GCS scores, only the first one on arrival at the hospital. Finally, the large percentage of missing data for both alcohol screen result and presence of other drugs should be considered and addressed. Because blood alcohol and drug measurements in emergency departments are likely biased towards intoxicated and incoherent patients. This can help explain the large percentage of missing data when it comes to these two variables. As mentioned previously, clinicians often will forget to draw a blood sample for alcohol and or drugs, and even if they do, these results may not be entered into the medical record or the registry in a timely and accurate manner. These variations in practice create a large proportion of missing data as it relates to alcohol and toxicology screens performed and documented. For purposes of this study, alcohol screen results were imputed, but as helpful as imputation can be to an analysis, it can also misrepresent the actual number of participants with a positive alcohol result thereby biasing the results.

Participants with a known history of substance abuse were found to have slightly higher GCS scores when compared to patients who did not. For every participant who had a history and a diagnosis of substance abuse, GCS scores increased by .075 units. Higher GCS scores indicated better neurological function and a less severe TBI. The study by Nguyen et al. (2014)

and Leskovan et al. (2020) explore the relationship between marijuana use, and alcohol, on mortality. The effect of marijuana on TBI severity is far less studied than alcohol, though pre-clinical studies have shown that the presence of marijuana is associated with some neuroprotective effects, including attenuated cell apoptosis, alleviation of cerebral edema, and improved cerebral blood flow (Leskovan et al., 2020). Further studies are needed to investigate the effects of marijuana on TBI severity alone, not when combined with alcohol or other substances.

These findings cannot be discussed without addressing the issue of missing data. Variables that influence GCS scores and TBI severity, such as alcohol screen result, sex, presence of drugs, history of cancer, history of mental and personality disorder, and history of alcohol abuse all had some element of missing data. All the aforementioned variables had less than 6% of the data missing, with some of them having less than 1% missing data (alcohol screen result 0.5%; sex 0.01%). Similarly, history of comorbid conditions all had less than 3% missing data. The two variables that had a large percentage of data missing were the presence of THC (66.1%) and the presence of other drugs (66.2%). Despite the missing data, both those variables were found to have a statistically significant influence on GCS scores, hence, TBI severity. Though statistically significant, the validity of those findings should be cautiously interpreted within the context of such large percentage of missing values for these hypothesized explanatory variables.

Aim 3E. One of the leading causes of injuries resulting in TBI incidence are collision related, such as motor vehicle or motorcycle crashes. Furthermore, almost half of the US states have legalized marijuana for medical use with some states allowing recreational use of marijuana. Therefore, collision type mechanism of injuries was examined to see if there was any

mediating influence on TBI severity in the presence of THC. It was determined that motor vehicle collisions did not influence, or mediate, the relationship between THC and TBI severity. However, motorcycle collisions suggested a partial influence on TBI severity. This was an expected result as studies have shown that head injuries are the leading cause of death in fatal motorcycle crashes (Du et al., 2020). It is therefore not surprising to see that GCS scores were reduced when motorcycle collisions were examined for mediating influences on TBI severity in the presence of THC. In one study by Steinemann et al. (2018), THC positivity among road traffic collisions in one US state tripled, with the number of THC positive patients presenting to the highest-level trauma center doubling. However, this data should be interpreted cautiously within the context of such large percentages of missing values for hypothesized explanatory variables. Finally, it is important to note the surprising finding that only 22 participants (0.4%) were found to have been involved in a motor vehicle collision, and only 16 (0.3%) were involved in a motor cycle crash. In the original data set, only 16,324 of 997,970 (1.6%) were involved in a motor vehicle collision, and 12,826 of 997,970 (1.3%) were involved in a motor cycle collision. In 2015, the CDC reported that more than 2.3 million people presented to the emergency department with motor vehicle-related injuries. Because not every single motor vehicle collision warrants a trauma activation or for the patient to be seen by a trauma surgeon, the number represented in the trauma registries would be much less. Hence, this may somewhat explain the lower numbers presented in the 2017 NTDB data set (CDC, 2017).

CHAPTER 7: LIMITATIONS AND CONLCUSION

Limitations

Several limitations of this study should be noted. Primarily, this study was a retrospective cohort study, therefore it may be missing potentially relevant data. Retrospective cohort studies,

though time efficient and cost effective, can be limited due to the nature of data collected. Missing data on several important predictor variables represents another drawback. The patient population in this study was heavily skewed towards moderate and severe TBI patients from one year of available data. A more evenly distributed sample over a longer time period with a larger number of moderate and severe TBI patients would provide more sensitive analyses.

The retrospective nature of this study limits the conclusions that can be determined as the methodology was not able to ascertain any measure of acute versus chronic marijuana use. Urine toxicology screens, such as those used in the ED, detectable levels of THC can be present for up to 4.6 days after the last noted use for individuals who do not use marijuana frequently, or up to 15.4 days after last use for those who are frequent users (Nguyen et al., 2014). Therefore, the presence of marijuana at the time of exposure may not correlate with recent use. Timing of exposure may be a factor and is an important limitation in this study. Additionally, study findings are based on patients with TBI that have had a urine THC test performed. Since not all patients with moderate or severe TBI were tested for the presence of THC, bias is thus introduced. There was a large percentage of study participants who were not tested or had missing test results for THC (undocumented or not resulted). Consequently, a more accurate analysis of THC prevalence and association was not possible as there was no way to determine which of those cases that were not tested or had no results documented were positive for THC. It is important to note that despite there being a small percentage of THC prevalence, this study reflects only one year worth of data, from 2017, and that establishing previous prevalence rates for comparison from the NTDB cannot be calculated. This is because the presence of THC was never abstracted nor documented in the data set prior to 2017. Future studies examining

prevalence rates for a series of years is warranted. Observational research has been shown to provide mis-estimations of the outcome of interest.

Data analyzed from the NTDB is extracted from various trauma registries across the United States and Canada. Each hospital employs its own registry abstractors who input the data collected from the electronic medical record into the registry which then feeds into the NTDB. This is an important limitation as the documentation and accuracy of data inputted may be inaccurate, incomplete, or inconsistent. This can result in information bias. Furthermore, systematic underreporting of data by participating hospitals can result in selection bias and create an inconsistent database. An example of this was the lack of consistency in the measurement and documentation of blood alcohol levels at time of hospital admission, and the missed opportunities for urine testing. This contributed to a large percentage of missing data which may have also introduced informational bias. Additionally, this variation in reporting results in incomplete data, as seen in this study, as well as conflicting data. There were two occasions where participants were documented as having not being tested for any substances yet were each found to have been positive for THC and/or cocaine. Outcomes of such practices and variations between trauma registries leads to a lack of confidence regarding data accuracy and resulting analyses.

Conclusion

Traumatic brain injury is a significant public health concern and a leading cause of death and disability. Many TBI patients have substance use exposure at the time of injury. This study aimed at examining the relationship between marijuana exposure at the time of injury and TBI severity in moderate and severely injured TBI patients. The study findings are timely as the number of states legalizing marijuana for both medical and recreational use increases. This

retrospective cross-sectional design study analyzed a large data set retrieved from the National Trauma Data Bank of patients with traumatic brain injury and the association between the presence of THC and brain injury severity, as defined by the GCS score. This is the first known study to examine the presence of THC at the time of injury and its effect on brain injury in a large demographic from a national dataset. The NTDB dataset captures 65% of all trauma hospitals capture; so, with some confidence the claim can be made that moderate and severe TBI, in this data set, are representative of the TBI population in North America.

This study found a smaller prevalence rate of THC presence in a purposive sample of TBI patients, but further studies are needed to estimate more accurate prevalence rates now that future datasets from the NTDB will delineate the types of substances tested. This will also allow for larger datasets to be analyzed which may yield different results. As is, the current dataset is not sufficient to establish strong analyses due to the large percentage of missing data, inconsistencies within the data itself, and limited to one dataset as previous datasets did not have the necessary drug information needed for analysis. The NTDB is the only database available that provides aggregated data on trauma patient populations. Despite the limitations inherent to retrospective studies and to databases such as the NTDB, findings from this study suggest an important link between the presence of a positive THC results and GCS score, hence TBI severity. Only one research study at the time of when the systematic literature review for this present study was done investigated the effects of THC presence in TBI patients and its influence on mortality. To date, there has been one identified study that investigated the influence of marijuana on TBI mortality (Leskovan, 2021).

When examining the differences between participants who tested positive for THC and those who did not, it was found that GCS scores were lower for those who tested positive, indicating a

more serious TBI. Additionally, participants who had a had a current diagnosis, or history of, cancer or substance abuse, were more likely to have tested positive for THC.

This study found that the presence of THC was significantly associated with lower GCS scores and a potentially more severe TBI; this relationship was significant without controlling for other predicting variables. Furthermore, a significant relationship was found between GCS scores, sex, blood alcohol levels, and a history of substance abuse at the time of presentation in the ED. Older participants were found to have higher GCS scores, indicating a less serious brain injury. Study participants who had higher blood alcohol levels were found to have lower GCS scores, indicating a more serious brain injury. Age and higher blood alcohol levels were found to be associated, with higher blood alcohol levels noted in younger patients.

A linear regression showed that the presence of THC was associated with lower GCS scores, which is a predictor of TBI severity. However, that finding was not statistically significant. Alternatively, being male, having elevated blood alcohol levels, having other drugs present on admission, and a history of substance abuse were all found to have a significant influence on GCS scores and TBI severity, with GCS scores being lower for all four variables, implying a more serious TBI.

To effectively determine the relationship between the presence of THC and TBI severity, better data, or datasets, are needed. Perhaps, the American College of Surgeons can be empowered to employ strategies to acquire more consistent data as it pertains to drugs, so that clean data is abstracted and inputted, and clean data is analyzed and then interpreted. Another important implication to consider is the inclusion of different variables and outcome measures that can help provide a better dataset for analysis. This can include diagnostic tests such as CT

scan findings, or mortality. However, the NTDB does not provide such data, therefore, the NTDB itself may not be the most ideal database to use to answer the research question posed.

As expected, and supported by other research studies, elevated blood alcohol levels, being male, presence of other drugs, and a diagnoses of substance abuse were found to have an influence on GCS scores. This confirms that these variables need to be considered in the context of TBI research.

While the presence of THC initially did show a hypothesized relationship to GCS score (with lower scores indicating higher TBI severity), the relationship became insignificant when adjusted for all the other covariates variables. As noted in the discussion section, and in the context of such large percentages of missing data in this study, validity of findings, such as THC prevalence rate in this TBI population, should be cautiously interpreted for all the included hypothesized explanatory variables. Further research with datasets that are larger and more complete are needed to fully understand and examine the relationship between marijuana and TBI severity. This study importantly underscores the need for better data to enable better research regarding the relationship between marijuana and TBI severity.

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