CURRICULUM VITAE

BIOGRAPHICAL

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EDUCATION and TRAINING

UNDERGRADUATE:

1999-2003	University of Wisconsin-Madison
	Bachelor of Arts, History

NURSING EDUCATION:

2007-2010	Allegany College of Maryland
	Associates of Science, Nursing
	Magna Cum Laude
2017-2018	Notre Dame of Maryland University
	Bachelor of Science, Nursing
2018-2020	Notre Dame of Maryland University
	Masters of Science, Leadership in Nursing Education
2020-	University of Maryland
	PhD, May 2024

AWARDS & HONORS

2008, 2009, 2010	Dean's List
2009, 2010	Phi Theta Kappa
2009	Derrick Memorial Nursing Scholarship

2010	Dorothy S. Hoehl Scholarship
2015	Shock Trauma Hero Award
2017	Award for Nursing Presence
2019	iQuERY Research Award
2020	Graduate Research Assistant Grant
2021	Graduate Research Assistant Grant
2022	Graduate Research Assistant Grant

APPOINTMENTS and POSITIONS

WORK EXPERIENCE:

2004-2006	MidAtlantic Regional Development Director
	The Huntington's Disease Society of America
	Baltimore, MD
2006-2008	The League for People with Disabilities
	Director of Development, Marketing & Public Relations
	Baltimore, MD
2008-2010	Garrett College
	Adjunct Instructor, English
	McHenry, MD
2010-2018	Johns Hopkins Bayview Medical Center
	The Johns Hopkins Burn Center
	Clinical Nurse, Burn Intensive Care Unit

2018-present	Johns Hopkins Bayview Medical Center
	The Johns Hopkins Burn Center
	Burn Program Coordinator
2019-2021	Notre Dame of Maryland University
	School of Nursing
	Clinical Instructor, Adult Health II
2020-2022	University of Maryland
	School of Nursing
	Graduate Research Assistant
2023	Johns Hopkins University
	School of Nursing
	Clinical Instructor, Synthesis
2023	Stevenson University
	School of Nursing
	Clinical Instructor, Adult Health II

CERTIFICATIONS

2010-current	Basic Life Support, Instructor
2010-current	Advanced Cardiac Life Support, Instructor
2010-current	Advanced Burn Life Support, Instructor
2016-current	Wound Treatment Associate
2023-current	Certified Burn Registered Nurse

MEMBERSHIPS in PROFESSIONAL and SCIENTIFIC SOCIETIES

American Burn Association

National Committee Member: Nursing Committee

National Faculty Member: Advanced Burn Life Support

Lead Nurse Planner

Board of Certification in Emergency Nursing

Board Member

Certified Burn Nurse Role Delineation Survey Committee Member

Certified Burn Nurse Exam Content Review Committee Member

Certified Burn Nurse Subject Matter Expert

Certified Burn Nurse Content Creator: Test Writing

Biomedical Advanced Research and Developmental Authority (BARDA), Resource Related Information Tracking Medical Communications Application (RITCA)

Special Advisor

PRESENTATIONS (POSTER)

2018 Werthman, E., Ware, L., Snyder, I. Evaluating Pressure Redistributing Surfaces for Prevention of Occipital Pressure Injuries. American Burn Association. Chicago, IL; April 2018

2019 Werthman, E. Can Prevention Strategies Increase Risk for Pressure Injuries? American Burn Association. Chicago, IL; April 2019

2019 Werthman, E. Do Worry About HAPI: Culture Change in the Burn Intensive Care Unit. iQuERY Conference. Baltimore, MD October 2019

2019 Werthman, E. Pressure Injury Prevention in the Burn Intensive Care Unit. Northeast Regional Burn Conference. Portland, ME. November 2019.

2022 Werthman, E., Cox, C., Caffrey, J. Nurse Driven Fluid Resuscitation in the Burn Center. American Burn Association. Las Vegas, NV; April 2022.

2022 Werthman, E., Cox, C., Lagziel, T. Why do elderly burn patients die? Analysis of early versus delayed ICU deaths, from 2014-2021. American Burn Association. Las Vegas, NV; April 2022.

2023 Rezwan, S. Ballou, J., Caffrey, J., Werthman, E. Burn Injuries During the Pandemic: Older Adults, Delays to Admission, and Longer Hospital Stays. American Burn Association. Dallas, TX. May 2023.

2023 Vocke, S., Andre, G., Caffrey, J., Dean, B., Werthman, E. Rehabilitation Time to Evaluation Report: A Quality Improvement Study. American Burn Association. Dallas, TX. May 2023.

2023 Werthman, E., Cox, C., Caffrey, J. Results of the Implementation of a Nurse Driven Fluid Resuscitation Protocol in a Regional Burn Center: A Mixed Methods Study. American Burn Association. Dallas, TX. May 2023.

PRESENTATIONS (LECTURE)

2012 Basic Burn Care, Annual Nurse Conference, Johns Hopkins Bayview Medical Center, Baltimore, MD

Basic Burn Care, Skin in September, Johns Hopkins Bayview Medical Center, Baltimore, MD

2014 Case Studies in Burn Care, Annual Nurse Conference, Johns Hopkins Bayview Medical Center, Baltimore, MD

2016 Case Study: 18-year-old Female with Traumatic Burn Injuries, MIEMSS Continuing Education Series, Shock Trauma Center, Baltimore, MD

2017 Burn and Wound Care, WOCN Society Meeting, St. Joseph's Hospital, Baltimore, MD

2017 Critical Care in the Burn Unit, Greater Washington Area Critical Care Nurses Society Annual Conference, Fairfax, VA

2017 Case Studies in Burn Care, MIEMSS Continuing Education Series, Shock Trauma Center, Baltimore, MD

2017 Case Study: Electrical Burn s/p MVC, Innova Fairfax Hospital, Fairfax, VA

2018 Chemical Burns, Johns Hopkins Hospital, Baltimore, MD

2019 Transfer of the Burn Patient, Sinai Hospital, Baltimore, MD

2019 Innovation in the Burn Center, iQuERY Conference, Johns Hopkins Bayview Medical Center, Baltimore, MD

2019 Grand Rounds, Transfer of the Critically Injured Burn Patient, UM Prince George's Hospital Center

2019 Culture Change in the Burn Center, Northeast Regional American Burn Association Conference, Portland, ME

2021 Society for Interdisciplinary Placebo Studies (SIPS). How Patients' Expectations and Long-Term Effects of Adverse Childhood Experiences Affect Burn Pain, Baltimore, MD (virtual, international)

2021 Paradigm Health Conference, Novel Therapies and Techniques in Skin Substitutes, Baltimore, MD (virtual, national)

2022 National Meeting of the American Burn Association. Pro/Con Debate: Nurse driven fluid resuscitation should be used in the burn center. Las Vegas, NV.

2023 National Meeting of the American Burn Association. Course director: Poster Rounds, Nursing

2023 National Meeting of the American Burn Association. Results of Nurse Driven Fluid Resuscitation.

2023 National Meeting of the American Burn Association. Moderator: Correlative IV: Nursing

2023 National Meeting of the American Burn Association Course director: Poster Rounds, Critical Care Nursing.

2023 National Meeting of the American Burn Association. Multidisciplinary Quality Improvement in the Burn Center Using Six Sigma and LEAN Methodologies.

PUBLICATIONS

Werthman, E., Lynch, T., Ware, L. & Caffrey, J. (2019). Evaluating pressure redistribution surfaces for the occiput. *Journal of Wound Care*:8, Sup9, S38-S41.

Werthman, E. In Smith, M.C., ed. (2020). *Nursing theories & nursing practice*. Philadelphia, PA: F.A. Davis.

Yesantharao P, El Eter L, Javia V, **Werthman E**, Cox C, Keenan J, Moseley R, Orosco

R, Cooney C, Caffrey J. Using Pressure Mapping to Optimize Hospital-Acquired Pressure Injury Prevention Strategies in the Burn Intensive Care Unit. *The Journal of Burn Care and Research.* In Press.

Friedmann, E., Gee, N., Simonsick, E., Barr, E., Resnick, B., **Werthman, E**., & Adesanya,I. (2021). Pet ownership and longitudinal change in physical function: Evidence from the BLSA. *Innovation in Aging*: 5: Sup1, S216–217. https://doi.org/10.1093/geroni/igab046.830

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Yoon, J. S., Khoo, K. H., Akhavan, A. A., Lagziel, T., Ha, M., Cox, C. A., Blanding, R., **Werthman, E. H**., Caffrey, J., & Hultman, C. S. (2022). Changes in Burn Surgery Operative Volume and Metrics due to COVID-19. Journal of burn care & research : official publication of the American Burn Association, 43(6), 1233–1240. https://doi.org/10.1093/jbcr/irac111

Moen, M., Doede, M., Johantgen, M., Taber, D., Adesanya, I., **Werthman, E.,** & Friedmann, E. (2023). Nurse-led hospital-to-community care, clinical outcomes for people living with HIV and health-related social needs. Journal of advanced nursing, 79(5), 1949–1958. https://doi.org/10.1111/jan.15485

Werthman, E., & Grand, A. (2023). Burn Nursing Specialty Certification: The Time Has Journal of burn care & research : official publication of the American Burn Association, 44(3), 740–741. https://doi.org/10.1093/jbcr/irad042

Abstract

Adversity in childhood is a well-known independent contributor to a variety of chronic illnesses including heart disease, diabetes, and obesity. In addition, adversity in childhood increase the risk of development of mental illnesses including anxiety, depression, substance use disorder. Recent lines of research have demonstrated that adversity in childhood also increases the risk of the development of chronic pain and alters the intensity of acute pain. Adversity in childhood is understood to be an important contributor to adult health, however, little is known about how childhood adversity impacts two specific types of pain: chronic orofacial pain and acute burn pain. In this dissertation, a literature review was conducted to examine how adversity in childhood had been explored in the burn population. A secondary data analysis was performed on a sample of phenotyped chronic orofacial pain to determine a relationship between childhood adversity and chronic temporomandibular pain. A study was then developed to examine this relationship in a sample of participants with acute burn pain.

Keywords: childhood adversity, pain, burn pain, orofacial pain

Characteristics of Pain in Survivors of Adverse Childhood Experiences

by
Emily Hunter Werthman

A dissertation submitted to the Faculty of the Graduate School of the
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Doctor of Philosophy
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To Delilah and Henry-who now know that you can do it all-if you have the support of an amazing partner

To Tom- for showing up every day to show them exactly what that looks like

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Chapter 1: Introduction to the problem

From the Latin, *poena*, meaning punishment, pain has historically been defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Merskey, 1979). In 2020, citing concerns for defining pain in a way that acknowledges its subjective nature, the IASP revised their definition by defining pain as "an aversive sensory and emotional experience typically caused by, or resembling that caused by, actual or potential tissue injury (Raja et al., 2020).The etymology of pain is useful in understanding pain after ACE exposure, as pain has been associated with punishment historically; "penal" shares the same root word. Children and adults with exposure to ACEs utilize self-blame to cope with their ACEs experience (Dorresteijn et al., 2019). This self-blame strategy is frequently carried forward to adulthood, where it impacts the biological and psychological experience of pain (Dorresteijn et al., 2019). There is a plausible link between psychogenic pain and the self-blame associated with ACEs (Kiecolt-Glaser, 1987). Chronic pain can be broadly classified as neurogenic and psychogenic (Morgan, Deuis, Frosig-Jorgensen, et al., 2018). Acute pain may be further classified as nociceptive, visceral, neurogenic, anticipatory, inflammatory, or psychogenic(Morgan, Deuis, Frosig-Jorgensen, et al., 2018). Unresolved pain increases catastrophizing, post-traumatic stress disorder (PTSD), anxiety, chronic pain, and depression(Van Loey, Klein-Konig, et al., 2018).

Adverse childhood experiences are "potentially traumatic events that occur in childhood" (Centers for Disease Control, 2020). More specifically, ACEs may be personal or familial. Personal ACEs include physical abuse, emotional abuse, verbal abuse, sexual

abuse, physical neglect, and emotional neglect (Centers for Disease Control, 2020). Familial ACEs include incarceration, alcoholism, mental illness, divorce, death, and the mother experiencing domestic violence (Oral et al., 2016).

Defining attributes: chronic orofacial pain

TMD is characterized by derangement of the jaw joint and/or muscles of mastication with a prevalence of 5-12% in the general population(Chisnoiu et al., 2015). TMD is known to disproportionately affect women, with a female-to-male ratio of 9:135 (Jivnani et al., 2019). Chronic orofacial pain is also widely acknowledged as a difficult pain disorder to treat (Ouanounou et al., 2017; Rodrigues et al., 2004; Yap et al., 2002). Current literature suggests that a multidisciplinary mind-body approach to management of TMD pain involving both pharmacologic and no-pharmacologic interventions improves clinical chronic pain(Cole & Carlson, 2018; Golanska et al., 2021; Vranceanu et al., 2012).

Defining Attributes: burn pain

The literature reveals three defining attributes of the burn pain concept. First, the pathophysiology of burn pain is complex and related to multiple pain pathways(Morgan, Deuis, Woodruff, et al., 2018). Second, because burn pain involves multiple pathways treatment is difficult and often requires multi-modal analgesia(Morgan, Deuis, Woodruff, et al., 2018). Lastly, when left untreated, burn pain contributes to the development of chronic pain and PTSD(Taal & Faber, 1997). The defining attribute of the literature exploring ACEs and pain is that patients with a history of ACEs experience pain differently, both biologically and psychologically(Dennis et al., 2019).

Background of the Problem

Adverse childhood experiences (ACEs) are loosely described as traumatic events that occur from birth through age 17 that impact the well-being of developing children and their health later in life. ACEs are broadly categorized into three subcategories: abuse, neglect, and dysfunction. More specifically, ACEs include physical, emotional and sexual abuse, as well as violence in the home, violence against a mother, and incarcerated relatives among others. While single events, such as a traumatic injury may be classified as an ACE, repeated exposure is thought to be more contributory. For example, a child who survives a severe car accident is less likely to be impacted by that single event than a child who has daily experience with domestic violence. Additionally, exposure to more than one category of ACE (i.e. incarcerated relative and domestic violence) is more impactful than exposure to a single category of ACE (i.e. incarcerated relative).

There is literature that explores the negative correlation between exposure to ACEs and adult health outcomes. In that literature, there is a quantifiable association between ACEs and recidivism, substance use disorders, post-traumatic stress disorder (PTSD), and chronic pain (Douglas et al., 2010). While ACEs impact the health and wellness of adults, their impact on health begins early. Nelson et al. go so far as to acknowledge a correlation between ACEs and the development of chronic pain in youth(Nelson et al., 2021). The scope of this problem is significant, with the Centers for Disease Control (CDC) reporting that 1 in 6 adults have experienced multiple ACEs and half of the top ten causes of death are associated with ACEs (CDC, 2019). In the burn population, where substance use disorders and pre-existing psychiatric diagnoses exist in large numbers, it has been hypothesized that the prevalence of ACEs may be higher than the general population.

Fassel et al., for example, found that nearly 40% of the burn sample explored in their study experienced at least one ACE, a rate higher than the state from which the sample was drawn(Fassel et al., 2019).

Gap in Knowledge

Extant literature has explored relationships between ACEs and multiple chronic health conditions, including pain. However, little is known about how pain catastrophizing may impact this relationship, both in chronic pain (chapter 3) and burn pain (chapter 4). Although their etiologies differ, TMD and burn pain are both multimodal, as the patient may experience nociceptive pain, inflammatory pain, neuropathic pain, functional pain, and anticipatory pain within the span of hours. Second, both types of are often linked to repeated, specific treatments/movements. In the case of TMD, pain may be related to specific repeated movements including talking, chewing, or sleeping. In burn care, pain may be related to specific repeated interventions including staple removal or splinting. As a result, anticipatory fear plays a large role in the experience of both TMD and burn pain. It is this concept of anticipatory fear that links the experience of chronic TMD and burn pain to ACEs.

To date, only one study has been published on the relationship between burn injuries and ACEs(Fassel et al., 2019). While Fassel et al.'s observational study explores the correlation between ACEs and burn outcomes, it only briefly discusses the relationship between these events and burn pain(Fassel et al., 2019). Moreover, this discussion focuses solely on numeric pain scores. There is not an attempt to describe the relationship between pain and ACE score. Similarly, although there has been literature exploring chronic pain

and ACEs, there has not yet been literature testing the causal relationship, particularly through the lens of patin catastrophizing as a mediator.

As no causal link between ACEs and burn pain has yet been postulated, the pathophysiology of burn pain in patients with a history of ACEs is also not well understood. The causal mechanism that is proposed to connect ACEs and pain is prolonged and repeated cytokine release during childhood traumas(You & Meagher, 2016). Adults with ACE history have baseline elevated levels of IL-6(Hartwell et al., 2013). Interestingly, burn patients experience a cytokine storm, with elevated IL-6 and IL-8 at approximately 48 hours post injury(Matsuura et al., 2019). Il-6 and Il-8 are both associated with heightened pain sensitivity(Gouin et al., 2017). It stands to reason that burn patients with ACEs will have even more elevated Il-6 and Il-8, causing higher levels of pain in this group. Current burn pain management does not account for differences in burn pain in patients with a history of ACEs, resulting in hypoalgesia in this population. The current failure to understand the mechanisms by which ACE exposure informs burn pain limits the ability to design effective analgesia protocols to prevent the occurrence of chronic pain and PTSD from hypoalgesia.

As with other types of pain when left untreated or undertreated, burn pain is not innocuous. In the short term, unresolved pain may result in refusal to participate in dressing changes and physical/occupational therapy(Perez Boluda et al., 2016). Long-term sequalae of these refusals include prolonged wound healing and contracture formation(Klifto et al., 2020), both of which have a demonstrable negative impact on quality of life(Spronk, Legemate, Dokter, et al., 2018; Spronk et al., 2019). Unresolved pain also increases catastrophizing and other psychological complications, including post-traumatic stress

disorder (PTSD), anxiety, chronic pain, and depression(Van Loey, Hofland, et al., 2018; Van Loey, Klein-Konig, et al., 2018). Physiologically, this link is explained by the massive release of cytokines and oxytocin during the inflammatory phase of the burn injury, as these chemicals are associated with pain intensity, stress, and anxiety(Van Loey, Hofland, et al., 2018).

The conceptual framework for this dissertation uses the biopsychosocial mode of pain first described by Engel(Engel, 1977). The biopsychosocial model of pain proposes that pain is a multi-factorial experience that humans experience physically, psychologically, and socially. In the proposed research study, the conceptual framework relies on the assumption that the concepts related to the phenomenon of burn pain after ACEs are the cytokine response after both ACEs and burn injury, catastrophizing and self-blame as coping techniques, and increased severity of pain following ACE exposure.

Children exposed to ACEs have been shown to have heightened levels of cytokines, including IL-6(Gouin et al., 2017). The cytokine storm associated with both physical and emotional trauma has been linked to heightened pain in both pediatric and adult trauma populations(Van Loey, Klein-Konig, et al., 2018). In addition to changing the way ACE patients appreciate pain, ACE exposure also contributes to the development of coping teachings that impact pain sensitization including catastrophizing and self-blame(Dorresteijn et al., 2019). Both strategies are then carried forward to adulthood, where it impacts the biological and psychological experience of pain(Dorresteijn et al., 2019). Indeed, Kiecolt-Glaser and Williams (1987) note there is a plausible link between severe, psychogenic pain experienced with burn injuries and the self-blame associated with ACEs.

The learned coping techniques of adult ACE survivors complicate the burn pain experienced as adults. The self-blame and catastrophizing that adult survivors of ACEs utilize as coping techniques(Dorresteijn et al., 2019), further increase cytokine release, thereby worsening pain severity. While most burn patients' cytokine storm ends within 72 hours of their injury, allowing for better pain management, this is not the case with ACE survivors. In the ACE population of pain patients, their coping strategies cause repeated cytokine storms, thereby increasing analgesia requirements, often not met by evidence-based guidelines developed for adults without trauma history.

Statement of the Problem

This dissertation aims to advance understanding of the relationship between ACEs and chronic pain (chapter 3), with a plan to utilize this foundational knowledge to explore the relationship between childhood adversity and burn pain (chapter 4). A better understanding of the differences in severity of burn pain in these patients will provide pathways for improved clinical outcomes associated with adequate analgesia. A thorough understanding of the concept of burn pain after ACEs, built upon a conceptual framework developed from the biopsychosocial model of pain, will allow for better treatment of acute burn pain, thereby reducing further injury (PTSD/chronic pain) and improving patient outcomes.

This dissertation seeks to fill a gap in knowledge related to the role of pain catastrophizing in chronic pain patients who have experienced childhood adversity. We then aim to use this foundational knowledge to design an elegant mixed-methods study exploring the experience of burn pain in adult survivors of ACEs. In doing so, the relationship between ACEs and pain will be fully explored, allowing for better

understanding of the overlap of the two concepts. Ultimately, the goal of this research is to provide opportunity to develop adequate pain relief for patients with ACEs, thereby lessening further traumatization in this patient population. Of note, the foundational research into the relationship between ACEs, chronic pain, and catastrophizing is the foundational research that is further explored in the relationship between between ACEs and burn pain, the latter of which is explored in the literature review in chapter two and the study design in chapter four of this dissertation.

Chapter 2: Adverse Childhood Experiences and Burn Pain: A Review of Biopsychosocial Mechanisms that May Influence Healing[1]

Abstract

Adverse childhood experiences (ACEs) impact over half of adults in the United States and are known to contribute to the development of a wide variety of negative health and behavioral outcomes. Although still largely unexplored, ACEs are an emerging concern in burn patients, who account for almost 450,000 hospitalizations in the United States annually. A literature search was conducted in CINAHL and PubMed to evaluate the role that ACE-induced changes in biological, psychological, and social processes may play in altering the experience of burn pain in adult survivors of ACEs. To date, research has focused on the role of ACEs in the development of chronic pain in patient populations that include individuals with gynecologic, orthopedic, or gastrointestinal conditions, but not individuals who have experienced burn injuries. Findings indicate that ACEs not only increase risks for chronic pain, but also influence emotional responses to pain in many of these individuals. These effects may be the result of neurobiological changes induced by ACEs during early development. However, further research is needed to understand the predictors and mechanisms that dictate individual differences in pain outcomes in patients with ACE exposure and to clarify the role that ACE-related alterations play in early healing and recovery from burn injuries.

Keywords: Expectancies; Early life; Stress; Symptom management; Coping

[1] Werthman, E. H., Colloca, L., & Oswald, L. M. (2022). Adverse childhood experiences and burn pain: a review of biopsychosocial mechanisms that may influence healing. *Pain reports*, *7*(4), e1013. https://doi.org/10.1097/PR9.0000000000001013

Background and Significance

Adverse childhood experiences (ACEs) impact over half of adults in the United States and are known to contribute to the development of a wide variety of negative health and behavioral outcomes (Jones et al., 2020). Originally defined by Felitti et al (1998), these experiences include events such as physical, mental, and sexual abuse, as well as neglect, divorce/separation, family incarceration, and violence, mental illness, or substance abuse in the home. There is emerging evidence that ACEs contribute to risks for chronic pain in both children and adults (Nelson et al., 2021; Salonsalmi et al., 2021) and are associated with increased severity of pain in medical conditions such as arthritis, back pain, and headaches (Sheinberg et al., 2019). In recent years, there has been growing interest in studying the biological mechanisms that may underlie these associations. Findings of several lines of research have provided evidence that individual differences in pain responses and risks for chronic pain may be the result of trauma-induced alterations in the developing brain and in key neurobiological sub-states, such as the hypothalamic-pituitary-adrenal (HPA) axis, and autonomic and immune systems (Burke et al., 2017; Gupta et al., 2019; Salberg et al., 2021; Zouikr & Karshikoff, 2017).

ACEs are an emerging concern in burn patients, who account for almost 450,000 hospitalizations in the United States annually (Association, 2021). Anecdotal evidence suggests that up to 40% of the adult burn population has had ACE exposure (Fassel et al., 2019). Yet, despite evidence that ACE exposure worsens pain outcomes in patients with other kinds of pain, only one published study has specifically explored the relationship between ACEs and burn injuries (Fassel et al., 2019). Findings showed that a history of ACEs predicted more depressive symptoms, less resilience, greater probability of post-

traumatic stress disorder (PTSD), and less social participation 3 months after burn injury. These findings provided preliminary evidence that ACE exposure may impact healing and coping following burn injuries. Although minimal differences in pain levels were observed between patients who reported > 4 ACE events as compared to those who reported < 4 events, several limitations of the study, such as the small sample size (N=34) and lack of power analysis, suggest that further research is needed to definitively establish the impact of ACE exposure on burn pain, healing and long-term morbidity and quality of life in burn patients.

Although the pathophysiology of acute burn pain is not yet fully understood, available data indicate that the mechanisms involve both peripheral and central processes and activation of nociceptive, neuropathic, and inflammatory pain pathways (Haddock et al., 2010; Kim et al., 2019; Klifto et al., 2020; Morgan, Deuis, Frosig-Jorgensen, et al., 2018; Retrouvey et al., 2020). In serious burn injuries, multiple surgical excisions occur during the initial hospitalizations, often with only days between procedures. Acute pain is, therefore, repeatedly experienced by the patient. Repeated wound care and dressing change procedures during periods of non-surgical intervention produce procedural pain, compounding the inflammatory process pain experienced during the initial cytokine storm (Klifto et al., 2020). In burn patients with large total body surface area (TBSA) injuries, surgical pain is complicated by additional procedural insults, causing prolonged cascading effects. Psychogenic pain has also been shown in burn patients, particularly among patients with traumatic burn injuries from self-immolation, assault, or accident (Rietschel et al., 2015). While it is generally assumed that the degree of pain that an individual experiences following a burn injury is determined by the severity and other characteristics of the burn

itself, growing evidence suggests that considerable variability in both acute pain responses and long-term morbidity may be due to individual factors that are unrelated to these factors (Edwards et al., 2007; Klifto et al., 2020; Spronk et al., 2019; Velmahos et al., 2019). Better understanding of these determinants could lead to improved trauma-related care and long-term physical and psychological outcomes of burn patients.

For the purposes of this narrative review, a conceptual model was developed to highlight selected biopsychosocial variables that could hypothetically influence responses to burn pain in persons with a history of ACEs (Figure 1). A literature search was conducted in CINAHL and PubMed for articles published between 2000 and 2021 using the biopsychosocial model to limit the search terms to Ace and: "burn," "burn pain"," pain", "peer group", "pain expectations", "pain and catastrophizing", "central sensitization", "epigenetics," "neurobiology," "hypothalamic-pituitary-adrenal axis," and "childhood adversity and HPA axis."

Potential biological mechanisms

Central sensitization. Central sensitization is characterized by a heightened responsiveness of the central nervous system which leads to hypersensitivity to both painful and innocuous stimuli (Sherman et al., 2015). This condition is observed in many chronic pain disorders and has been used to explain both increased intensity of pain in patients with a history of trauma and chronic pain (Mansiz-Kaplan et al., 2020), and heightened affective responses to pain (Johnson et al., 2020; Lumley et al., 2011). Importantly, functions of brain regions, such as the prefrontal cortex, amygdala, and nucleus accumbens, which are involved in both central sensitization and the affective components of pain, are significantly altered by ACEs (Herzberg & Gunnar, 2020).

Amygdala-prefrontal circuits have been shown to be particularly sensitive to the effects of environmental influences early in life, which may result in regional changes that persist well into adulthood (VanTieghem & Tottenham, 2018). Although very few studies have directly examined the involvement and consequences of such changes with respect to pain, there is evidence that early life adversity leads to altered functional activation of nodes within central pain pathways in rats, which are proposed to be related to central amplification of sensory input (Holschneider et al., 2016). Changes induced by early life adversity in these regions (e.g., thalamo-cortico-amygdala pathway) have also been shown to lead to exacerbated pain sensitivity in animal models (Salberg et al., 2021). Studies focusing on the effects of ACEs on pain circuits in humans are still sparse. However, ACE-related alterations in intrinsic connectivity in patients with chronic abdominal pain has been observed within the salience/executive control network, which is implicated in the pathophysiology of central pain amplification (Gupta et al., 2019). A dose-risk relationship has also been observed between ACE history and central sensitivity in several chronic pain syndromes (Jones, 2016).

It is notable that in burn patients, there is evidence that central sensitization within the spinal cord, which seems to be part of the long-lasting changes in neuronal and nonneuronal tissue damage from burns, contributes to excessive pain following burn injuries (Patwa et al., 2019). Although links with burn pain are speculative, Chung et al. (2007) showed that maternal separation upregulates activity of ascending pathways at the spinal level as well as the thalamo-cortico-amygdala pathway in rats, which contributed to sensitization. Thus, it is possible that the effects of burn injuries could be intensified in pathways that have already been sensitized by ACEs. Post burn inflammation in

combination with increased ACE-related neuroinflammation (Salberg et al., 2020) could also potentially contribute to central sensitization and its accompanying hyperalgesia through upregulation of IL-8 and centrally mediated hyperalgesia (Morgan, Deuis, Frosig-Jorgensen, et al., 2018).

Hypothalamic-pituitary-adrenal (HPA) axis function. The HPA axis is a complex system that mediates the body's endocrine response to stress through a series of hormonal responses that ultimately lead to the release of glucocorticoids from the adrenal cortex. Animal models simulating psychological ACEs through maternal deprivation (MD) or maternal separation have demonstrated that early life trauma is associated with profound and enduring changes in HPA axis function (Maccari et al., 2014). Both hypercortisolemia and hypocortisolemia have been reported in humans with a history of ACEs, which have been shown to contribute to increased stress reactivity and vulnerability for a host of psychopathological, metabolic, and chronic inflammatory conditions (Brydges et al., 2014; Raison & Miller, 2003; Womersley et al., 2021).

Importantly, one consequence of such HPA axis dysregulation is increased vulnerability for the development of chronic pain (Vachon-Presseau et al., 2013). It has been suggested that enhanced salivary cortisol secretion is associated with greater pain intensity in response to acute pain; however, hypocortisolemia may be a marker for pain chronicization (Nees et al., 2019). Increased demand on the HPA axis during the acute recovery from a burn injury alters the stress response (Palmieri et al., 2006). In fact, Akita and colleagues showed that HPA axis activity is a good marker of disease severity and prognosis in patients with extensive burns (Akita et al., 2006). Although little is known about the influence of HPA axis function on burn *pain*, there is evidence that 8 weeks of

cortisol administration via drinking water is coupled with thermal hyperalgesia in rodents (Hache et al., 2012). Taken together, these findings suggest that pre-existing alterations in HPA axis function resulting from ACE exposure could be mechanistically linked to disadvantageous outcomes following a burn injury in adults with this history. This would be consistent with notions that prolonged activation of stress systems contributes to central sensitization and exacerbated responses to pain and noxae.

Immune system function. Findings of a growing body of research have shown that ACEs are associated with increased activation of the immune system, which is associated with susceptibility to inflammatory disease and exaggerated responses to injury in later life (Burke et al., 2017). Ganguly and Brenhouse (2015) suggested that early life adversity precipitates deleterious suppression of inflammatory markers during early development but causes a shift toward a proinflammatory state later in life. There is evidence of alterations in peripheral markers, such as IL-6, TNFα, C-reactive protein, and leukocytes in ACE-exposed individuals (Brydges & Reddaway, 2020). Alterations in neuroinflammatory gene expression in brain regions associated with pain and mood have also been observed (Burke et al., 2017).

Zouikr and Karshikoff (2017) suggested that the immune system has a profound effect on pain systems throughout life via neuroimmune and neuroendocrine interactions. Findings from several lines of preclinical studies indicate that dysregulation of immune function early in life may lead to long-lasting hyperalgesia, enhanced nociceptive behavior to inflammatory stimuli, and altered nociceptive processing, which together suggest sensitization of nociceptive circuits (Burke et al., 2017). Findings from both preclinical and clinical studies have shown that burns cause an acute inflammatory response that can be

either restricted to the site of injury or involve systemic inflammatory processes (Morgan, Deuis, Frosig-Jorgensen, et al., 2018). The cytokines and inflammatory molecules that are released mediate wound healing contribute to burn-related allodynia and hyperalgesia. Thus, although the research has yet to be conducted, it is reasonable to speculate that an immune system that has been dysregulated by ACE exposure could increase the patient risk for significant morbidity and pain following a burn injury.

Epigenetic changes. Broadly defined, epigenetic mechanisms are processes, such as DNA methylation, chromatin remodeling, or histone posttranslational modification, that regulate gene expression without changing the genetic code (Levenson & Sweatt, 2005). Accumulating evidence suggests that epigenetic mechanisms mediate the long-term effects of ACEs on the function of the HPA axis and stress-sensitive brain regions (Brydges et al., 2014; McGowan et al., 2009; Myers et al., 2014; Tyrka et al., 2016), which may play a pivotal role in the etiology of several neuropsychiatric, neurodegenerative and autoimmune illnesses (Deyo et al., 2016).

Interestingly, epigenetic mechanisms involving stress-related genes have also been shown to be involved in the development and maintenance of persistent pain states (Geranton, 2019). One gene whose function has been shown to be altered by early trauma is the stress regulator FKBP5 (FDBP Prolyl Isomerase 5). FKBP5 is an important modulator of the stress response, helping to regulate not only glucocorticoid receptor activity, but also a multitude of other cellular process in the brain and periphery. Interactions between FKBP5 and environmental stressors have been shown to contribute to a number of aberrant phenotypes in both rodents and humans (Zannas et al., 2016). Importantly, this gene also seems to play an important role in nociceptive processing,

regulating chronic pain states through modulation of glucocorticoid signaling (Maiaru et al., 2016). Collectively, these findings suggest that the epigenetic changes induced by ACEs could underlie the impact of early adversity on both the emotional responses to pain and susceptibility to developing chronic pain later in life (Burke et al., 2017). Although little is known about these relationships in burn patients, one could postulate that the dysregulation of metabolic processes and cortisol regulation that occurs following severe burns might interact with alterations induced in the FKBP5 gene to increase susceptibility for chronic pain.

Potential psychological mechanisms

Expectancies/Expectations. Expectancies are psychophysical predictions of future events and can occur without full awareness (i.e. implicit expectancies). On the contrary, expectations refer to conscious cognitive dynamic constructs referring to predictions of future events and outcome anticipations that can measured via validated scales and verbal self-reports (L. Colloca et al., 2020; Okusogu & Colloca, 2019). Expectations as predictors of future outcomes can be positive and negative and can affect neural pain processes (L. Colloca et al., 2020; Colloca & Miller, 2011; Colloca et al., 2019). In orthopedic patients, for example, particularly knee and hip replacement patients, belief in treatment efficacy (positive expectations) has been associated with lower pain scores and better patient outcomes (Kastner et al., 2021). Positive and negative expectancies influence outcomes by driving behavioral and neurobiological pain systems and processes (Colloca et al., 2019). Expectations of positive or negative outcomes are often not met in daily clinical practice. We demonstrated that expectation violation expressed as a misalignment between what it is expected and what is actually experienced, alerts

responses to pain. Such discrepancies resulted in the activation of the left inferior parietal cortex that redirects attention load in the presence of misalignment between sensorial stimulations and cognitive events in healthy participants (Colloca et al., 2019).

Expectations are dynamic in nature and, therefore, can be shaped to optimize outcomes. Rief et al. (2017) conducted a trial preoperatively to optimize patient expectations to improve long-term outcome in heart surgery patients. The study was designed as a three-arm randomized clinical trial including a follow-up of six months in 124 patients undergoing coronary artery bypass graft surgery. The three arms included a short-lasting psychological pre-surgery session with the scope to optimize outcome expectations (EXPECT); a psychological control session which focused on emotional support and general advice only (SUPPORT); and a standard medical care session. Both pre-surgery sessions were comparable in duration. The authors demonstrated that a brief session tailored explicitly to optimize expectations improved disability up to 6 months after surgery. This study along with many others from this team pave the way to psychological approaches that align expectations to optimize long-term outcomes even in the presence of invasive surgical interventions and other procedures (Gasteiger et al., 2018; Heisig et al., 2015; Laferton et al., 2017).

While the role of changing expectations has not yet been validated in patients experiencing burn injuries, the idea of aligning expectations with healing prognosis is important in injuries that require prolonged and/or repeated hospitalizations. Walton et al. (2021) found that high ACE scores together with threat appraisal were associated with increased expectations that events would be painful and/or traumatic in patients with acute, musculoskeletal trauma. Although causation could not be inferred from the cross-sectional

data, the findings were consistent with those of animal studies showing effects of early life trauma on threat processing. Overall, the findings extended notions that subjective expectations related to pain are shaped entirely by the acute trauma event, highlighting the role that pre-existing vulnerabilities or resilience may play in the process. Further research into the role expectations play in the experience of acute burn pain in adult survivors of ACEs could potentially help to substantiate the proposed pathways.

Pain catastrophizing. Pain catastrophizing (PC) has been defined as a maladaptive orientation toward actual or anticipated pain (Gatchel et al., 2007) that has three distinct characteristics: rumination (inability to inhibit pain-related thoughts), magnification (exaggerated threat value of the pain stimulus), and helplessness (Sullivan et al., 2005). Catastrophizing is a strong predictor of disability in patients with chronic pain (Subramanian & Venkatesan, 2021; Varallo et al., 2021) and has been associated with several dimensions of the pain experience, including heightened affective responses (Varallo et al., 2021), increased severity (Kadimpati et al., 2015; Kanzawa-Lee et al., 2018), and longer duration (Brecht & Gatchel, 2019). Not surprisingly, given its links with affective responses to pain, PC is also associated with depression and anxiety ((Darnall & Colloca, 2018; Sturgeon et al., 2017) and, in fact, may mediate relationships between psychological distress and pain experiences (Cassar et al., 2018; Pinto et al., 2012). Findings of one recent brain imaging study showed that several brain regions involved in PC are also involved in mood regulation and pain processing (Hubbard et al., 2014; Seminowicz & Davis, 2006), which, at least in theory, could help to explain these relationships.

Strong associations have also been observed between child maltreatment and PC. In one study, the relationship was shown to be independent of other risk factors, including anxiety and depression (MacDonald et al., 2021). Reported relationships between ACEs and PC include all three dimensions of PC and several different types of ACEs, although emotional abuse seems to show the strongest association (Pieritz et al., 2015; Sansone et al., 2013; Ziadni et al., 2021). While there has been only limited study of PC in burn patients, evidence of a relationship with pain sensitization and duration has been reported (Haythronthwaite et al., 2001). Van Loey, Klein-Konig, et al. (2018) further found that pain catastrophizing 6 months following a burn injury predicted both chronic pain and symptoms of post-traumatic stress disorder (PTSD) at 12 months post-burn. This suggests that screening for a history of child maltreatment and tendency to catastrophize could lead to early identification of individuals who are at greater risk of developing PTSD and chronic pain following a burn injury. However, to date, PC affects acute burn pain has not been explored in burn patients with ACEs.

Potential influences of social learning

Peer group. Peer groups are often discussed in ACE literature as both moderating and mediating the impact of ACE exposure, particularly on normal development in adolescence (X. Wang et al., 2020). Explorations of the relationship between ACEs and deviant peer groups have demonstrated that exposure to ACEs predisposes adolescents to seek out and develop such peer groups (Trinidad, 2021).

Involvement in deviant peer groups has been shown to lead to further trauma and have been linked to poor health outcomes. The converse, that supportive peer groups for survivors of ACEs are associated with better outcomes, has also been demonstrated

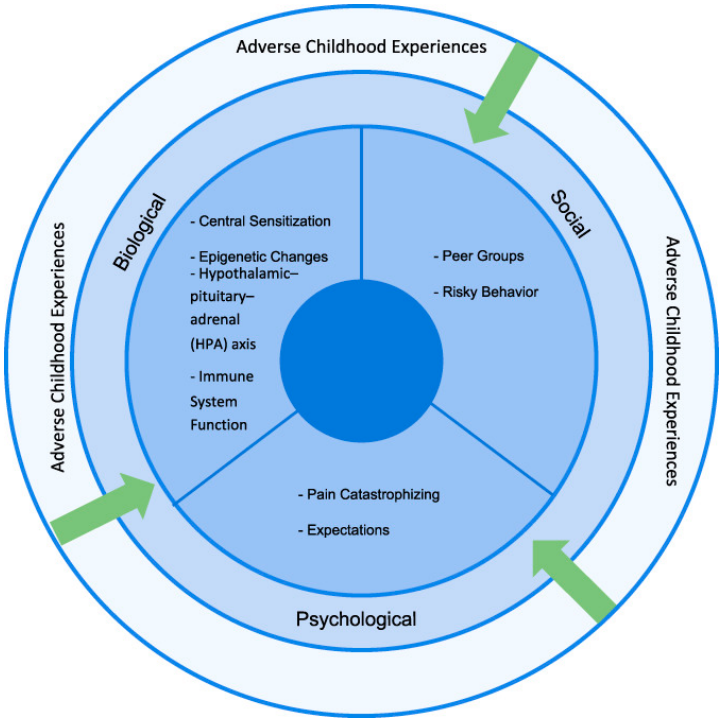
(Karatekin & Ahluwalia, 2020). Supportive peer groups need not always take the form of same-age peers, but can be fulfilled with supportive older adults or communities (D. Wang et al., 2020). In adult burn patients, who may have significant barriers to inclusion in adult peer groups due to scarring from catastrophic injuries, the consequences of exclusions from adolescent peer groups and/or inclusion in deviant peer groups may be compounded. Further research into how deviant or nonexistent peer groups for adult survivors of ACEs impacts their affiliation with adult peer groups and the experience of pain is warranted.

Conceptual framework

The biopsychosocial model of pain, which guided us in writing this review, hypothesizes that pain is dependent on interconnected biological, psychological, and social variables specific to the individual experiencing pain (Haythronthwaite et al., 2001; Meints & Edwards, 2018). As such, the model allows for exploration of the complex mechanisms by which ACE exposure colors the experience of acute and chronic burn pain in survivors of childhood adversity (Figure 1). In the biological domain, these mechanisms may include central sensitization, alterations in HPA axis and immune functions, and changes in epigenetic processes. Although examination of the effects of trauma on the development of central sensitization and epigenetic processes are relatively new areas of inquiry, there is a growing body of literature supporting the important role that both play in the experience of acute pain and the development of chronic pain. In the psychological domain, a small body of evidence has demonstrated that ACE exposure may influence expectations related to painful experiences, as well as tendencies for pain catastrophizing, which may in turn heighten risks for adverse outcomes related to pain. Finally, although not yet studied with respect to pain, in the social domain, there is evidence that ACE exposure may be

associated with greater tendencies to seek out deviant peer groups, which may also be linked to poor health outcomes.

Figure 1, Conceptual model



Taken together, these findings highlight several etiological pathways that may help to explain relationships between a history of ACEs and adverse pain-related outcomes in adulthood. What is remarkable in this review, however, is the paucity of research that has explored these relationships in patients with burn injuries. Not only has there been minimal research exploring the consequences of ACE exposure in burn patients, but there has been little investigation of the biological, psychological, or social mechanisms that may underlie individual differences in pain experiences and response to treatment in these individuals, regardless of cause. The evidence from human laboratory and clinical studies showing that ACEs alter perceptual and affective responses to other kinds of pain support theories that

the pathways and assumptions described in this paper may hold true for burn patients. Moreover, what we do know about the unique physiology and psychological ramifications of burns, suggests that the consequences of ACE exposure may be compounded in these individuals. Post-burn inflammation and the high demand on HPA axis and brain stress systems during acute recovery from burns, for example, may interact with pre-existing deficits inflicted in these systems by ACE exposure to significantly impact recovery. Given that ACE exposure has also been associated with greater catastrophizing and more negative expectations related to pain, it might also be expected that ACE exposure would be associated with greater psychological morbidities in burn patients. Burn injuries are among the most painful experiences that individuals can encounter, treatments often contribute to ongoing occurrences of acute pain, the duration of pain and disability from these injuries can last from months to years, and the pain is often accompanied by psychological trauma and alienation from significant others.

Conclusion

Pain may remain an ongoing source of disability long after the acute recovery period is over in burn patients. Further research is needed to understand the predictors and mechanisms that dictate individual differences in outcomes. It is our hope that better understanding of the relationship between ACEs and burn pain will help to improve the prognostic, diagnostic, and clinical management of burn patients and support the development of novel approaches to pain management that target the as yet unspecified pathways activated by ACEs in ACE-exposed individuals who experience a burn injury.

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Chapter 3: Pain after adversity: Chronic orofacial pain and pain catastrophizing in adult survivors of childhood adversity

Abstract

Early life stress produces changes in the endogenous opioid system (Melchior et al., 2022), that predispose survivors of adversity to the development of chronic pain(Burke et al., 2017). In chronic pain patients, early life stress produces hyperalgesia and pronociception (Jennings et al., 2014). The dose of ACE exposure is known to impact not only overall health, but the intensity of pain (Dennis et al., 2019). This paper explores how pain catastrophizing (PC) in chronic pain patients varies as measured by ACE-IQ score.

Keywords: pain catastrophizing, orofacial pain, childhood adversity, ACE

Introduction

Temporomandibular Disorder (TMD) is a disease process involving the derangement of the jaw joint and/or muscles of mastication that affects up to 15% of the general population (Macri et al., 2022). TMD disproportionately affects women and young adults and has been linked to physical (Chisnoiu et al., 2015), psychological (Restrepo et al., 2021), and hormonal changes (Robinson et al., 2020). TMD is also associated with pain, significantly contributing to quality of life. Pain is a biopsychosocial condition that is influenced by biologic, psychologic, and social factors that mediate the patient's perception of pain (Engel, 1977). As such, multimodal analgesia techniques for TMD pain include medication (Ouanounou et al., 2017), rest (Rodrigues et al., 2004), and heat application (Khairnar et al., 2019) have limited usefulness in patients with severe TMD (Meyer, 2017). At present, although anxiety (de Resende et al., 2020), depression (Manfredini et al., 2010), and other mental health diagnoses (Gatchel et al., 1996; Kleykamp et al., 2022; Yap et al., 2002) are known to impact the experience of TMD, the role of adversity in childhood in facilitating the occurrence of the disorder, has not yet been fully explored. Adverse childhood experiences (ACEs) have been identified as a risk factor for the development of pain and opioid use disorders in many patient populations (Spronk, Legemate, Oen, et al., 2018). Additionally, a link has been established between ACEs and central sensitization (Mansiz-Kaplan et al., 2020), a known contributor to the development of chronic pain. ACE-related changes in pain severity in individuals with chronic abdominal (Holschneider et al., 2016) and gynecologic pain have been observed (Gupta et al., 2016). Although not yet fully understood, changes in the HPA-axis and endogenous opioid system may be responsible for these alterations (Burke et al., 2017). Given the

prevalence of TMD in younger adulthood, the traumatic experiences of childhood and adolescence, may prove to be an important consideration in designing effective psychological components of a multimodal analgesia program.

Childhood adversity, a psychosocial factor known to influence the experience of pain (You & Meagher, 2016), is commonly measured through the ACE-10 (Felitti et al., 1998) or ACE-IQ tool (Organization, 2011). ACEs are also a significant threat to the 61% of Americans who experience them, with five of the top ten causes of death in adults related to ACE exposure (Dowell D, 2016). Studies focusing on the effects of ACEs on pain phenotypes in humans are still sparse. However, ACE-related alterations in intrinsic connectivity in patients with chronic abdominal pain has been observed within the salience/executive control network, which is implicated in the pathophysiology of central pain amplification (Jones, 2016). A dose-risk relationship has also been observed between ACE history and central sensitivity in several chronic pain syndromes (Maunder et al., 2017). ACE exposure also worsens chronic pain, (Mansiz-Kaplan et al., 2020; Maunder et al., 2017) risk of opioid dependence, (Mansiz-Kaplan et al., 2020; Maunder et al., 2017) and pain catastrophizing (PC) (MacDonald et al., 2021; Sullivan et al., 2005; Van Loey, Klein-Konig, et al., 2018; Ziadni et al., 2021). Understanding whether ACE exposure impacts pain severity in these chronic pain subjects can provide valuable insight into how ACEs may mediate pain.

Importantly, early life stress produces changes in the endogenous opioid system (Melchior et al., 2022), that predispose survivors of adversity to the development of chronic pain (Burke et al., 2017). In chronic pain patients, early life stress produces hyperalgesia and pronociception (Achenbach et al., 2019; Chung et al., 2007; Holschneider et al., 2016).

Strong associations have been observed between child maltreatment and PC (MacDonald et al., 2021; Ziadni et al., 2021). In one study, the relationship was shown to be independent of other risk factors, including anxiety and depression (MacDonald et al., 2021). Reported relationships between ACEs and PC include all three dimensions of PC (magnification, rumination, and helplessness) and several different types of ACEs, although emotional abuse seems to show the strongest association (Pieritz et al., 2015; Sansone et al., 2013; Ziadni et al., 2021). As yet, the relationship between ACEs, pain catastrophizing, and chronic pain has not been established. It is plausible that ACEs might facilitate chronic pain via elevations of pain catastrophizing. Herein, we examine how pain catastrophizing in participants with confirmed chronic pain diagnoses varies with respect to ACEs exposure. This study examines sociodemographic and psychological factors that affect chronic orofacial pain, demonstrating that pain catastrophizing mediates these relationships.

Methods

Using data from a large parent study in TMD (L. Colloca et al., 2020), the purpose of this study was to determine how pain catastrophizing varies respective to exposure of childhood adversity in a sample of chronic orofacial pain patients. The parent study was an IRB-approved experimental study.

Participant Recruitment

Participants were recruited using advertising in local newspapers, student list, regional orofacial pain primary care providers, Craigslist, participant recruitment, pain management clinics, previous research participants, flyers at local businesses, advertising on public transportation, and advertising on social media such as X (formerly known as

Twitter), Instagram and Facebook. A sample of 402 participants were enrolled from these efforts, of whom five were removed due to data incompleteness (Table 1). Participants gave verbal and written informed consent to participate prior to the in-person eligibility screening. All study procedures were approved by the University of Maryland, Baltimore Institutional Review Board (IRB Protocol # HP-00068315) and were conducted in accordance with the Declaration of Helsinki. Participants were compensated $100 via check or gift card for completion of all study procedures.

Setting

The study was conducted in the clinical testing suite at the University of Maryland School of Nursing (SON). All of the analyses performed herein were conducted as part of a secondary data analysis.

Procedure

For all participants, TMD diagnosis was confirmed using the TMD diagnostic criteria and a clinical examination by an independently trained, calibrated examiner according to the Axis I Diagnostic Criteria for TMD (DC/TMD) (Schiffman et al., 2014). Once TMD was confirmed, participants were enrolled in the study.

Measures

In addition to heart rate, blood pressure, and other physical measures of pain, a variety of psychological questionnaires were administered to each participant including ACE-IQ(Organization, 2011) (Table 2), pain catastrophizing (Sullivan et al., 1995), Graded Chronic Pain Scale (GCPS) (Dixon et al., 2007), the Depression, Anxiety & Stress Score (DASS-21)(Henry & Crawford, 2005), Positive and Negative Affect Scale (PANAS)(Watson et al., 1988), and the Revised Life Orientation Test (LOT-R) (Scheier

et al., 1994). Quantitative sensory testing was also conducted to determine each participant's pain threshold and pain tolerance.

ACE-IQ Childhood adversity was assessed using the Adverse Childhood Experiences International Questionnaire (ACE-IQ)(Organization, 2011). The ACE-IQ is derived from the original ACE tool which was developed for use in the Unites States (Felitti et al., 1998). The ACE-IQ was developed by the World Health Organization for use in all countries (Organization, 2011). It measures ACEs, the association between them, and risky behaviors later in life and is designed for use in adult populations. Questions assess family dysfunction, physical, sexual, and emotional abuse and neglect, peer violence, community violence, and collective violence. Participants are asked about the circumstances of their childhood, with a score of 1 assigned to circumstances indicating adversity (household violence, physical abuse etc.). Scores range from 0=no adversity to 13=high level of adversity (Organization, 2011). The ACE-IQ assesses physical abuse (2 questions), emotional abuse (2 questions), sexual abuse (4 questions), alcohol/drugs (1 question), incarcerated family member (1 question), mental illness (1 question), household violence (3 questions), one or no parents (2 questions), emotional neglect (2 questions), physical neglect (3 questions), bullying (1 question), community violence (3 questions), and collective violence (4 questions). A total ACE score out of 13 was calculated for each participant by summing responses to each question. The 13 individual ACEs are described herein.

Physical abuse is having been spanked, slapped, kicked, punched, or beaten up by a household member; or having been hit or cut with an object by a household member.

Exposure was identified if the participant responded “once,” “a few times,” or “many times” to one or more of the questions in this category(Organization, 2011).

Emotional abuse is having been insulted, humiliated, yelled at, screamed at, or sworn at by a household member; or as having been threatened to be abandoned or thrown out of the house by a household member. Exposure was identified if the participant responded “once,” “a few times,” or “many times” to one or more of the questions in this category.

Sexual abuse is having been touched or fondled by someone in a sexual way when it was not wanted; having been forced by someone to touch their body in a sexual way when it was not wanted; having had someone attempt oral, anal, or vaginal intercourse when it was not wanted; or having had oral, anal, or vaginal intercourse with someone when it was not wanted. Exposure was identified if the participant responded “once,” “a few times,” or “many times” to one or more of the questions in this category.

Alcohol/drug exposure is having lived with a household member that was an alcoholic or misused street or prescription drugs. Exposure was identified if the participant responded “yes” to this question.

Incarcerated family member is having lived with a household member who was ever sent to jail or prison. Exposure was identified if the participant responded “yes” to this question.

Mental illness is living with a household member who was depressed, mentally ill, or suicidal. Exposure was identified if the participant responded “yes” to this question.

Household violence is having seen a household member being insulted, humiliated, yelled at, screamed at, or sworn at; having seen a household member being slapped, kicked, punched or beaten up; or having seen a household member being hit or cut with an object.

Exposure was identified if the participant replied “once,” “a few times,” or “many times” to one or more of the questions in this category.

One or no parents is as having parents that were separated or divorced; or having a mother or father that passed away. Exposure was identified if the participant responded “yes” to one or more of the questions in this category.

Emotional neglect is parents/guardians who do not understand problems and worries; or having parents/guardians do not really know what the participant were doing with their free time when not at school or work. Exposure was identified if the participant responded “never” to one or more of the questions in this category.

Physical neglect is parents/guardians not providing food even when they could easily have done so; parents/guardians being too intoxicated by drugs/alcohol to provide care; or parents/guardians not sending the participant to school even when it was available. Exposure was identified if the participant responded “once,” “a few times,” or “many times” to one or more of the questions in this category.

Bullying is having been the target of threats, intimidation, or violence in peer groups. Exposure was identified if the participant responded “once,” “a few times,” or “many times” to the question in this category.

Community violence is as having seen or heard someone being beaten up in real life; having seen or heard someone being stabbed or shot in real life; or having seen or heard someone being threatened with a knife or gun in real life. Exposure was identified if the participant responded “once,” “a few times,” or “many times” to one or more of the questions in this category.

Collective violence is defined as having been forced to go and live in another place due to wars, terrorism, or organized violent crime; having experienced the destruction of a home due to wars, terrorism, or organized violent crime; having been beaten up by soldiers, police, militia, or gangs; or having a family member or friend killed or beaten up by soldiers, police, militia, or gangs. Exposure was identified if the participant responded "once," "a few times," or "many times" to one or more of the questions in this category.

Given the sensitive nature of the ACE survey, participants had the option to respond "refuse to answer" for any question that might have been too traumatic or difficult for them to answer. "Refuse to answer" cases ranged from 6 participants ("Did your parents/guardians really know what you were doing with your free time when you were not at school or work?") to 26 participants ("Did someone actually have oral, anal, or vaginal intercourse with you when you did not want them to?"). Participants cases with "refuse to answer" were omitted from analyses for those specific ACE-IQ questions.

Pain catastrophizing scale (PCS) Pain catastrophizing (PC) was assessed using the Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995). Participants indicated the degree to which they experience certain thoughts and feelings while in pain. These questions are answered using a 5-point scale (0 = Not at all, 4 = All the time), and answers are summed for a total score between 0 and 52. The rumination subscale is the subtotal of questions 8 to 11; the magnification subscale is the subtotal of questions 6, 7, and 13; and the helplessness subscale is the subtotal of questions 1 to 5 and 12. Higher scores indicate higher levels of PC and its dimensions. Rumination is a continued focus on the negative condition of pain (Leung, 2012). Magnification refers to the tendency to disproportionately

elevate the perceived threat of a stimulus(Leung, 2012). The helplessness subscale measures the tendency to feel helpless in the context of pain (Quartana et al., 2009).

Graded Chronic Pain Scale (GCPS) The GCPS is validated tool to quantify the degree of pain severity and interference in orofacial pain patients in the past month (Dixon et al., 2007). Pain severity is based on three questions assessing current pain, worst pain in the last month, and average pain in the last month on an 11-point scale (0 = no pain, 10 = pain as bad as could be). A total pain severity score is calculated by multiplying the average of the 3 responses by 10. Pain interference is based on 3 questions assessing interference in daily activities, social/recreational activities, and work activities in the last month on an 11-point scale (0 = no interference, 10 = unable to carry on any activities). A pain interference score is calculated by multiplying the average of the 3 responses by 10.

Participants are also asked to report how many days out of 30 that pain interfered with their daily functioning. Disability points are assigned based on the interference score and the number of days pain interfered with their daily functioning. Interference score of 0 to 29 is worth 0 points, score of 30 to 49 is worth 1 point, score of 50 to 69 is worth 2 points, and score of 70 or more is worth 3 points; interference for 0 to 1 day is worth 0 points, 2 days is worth 1 point, 3 to 5 days is worth 2 points, and 6 or more days is worth 3 points. These points were summed for a total disability score.

Depression, **Anxiety, and Stress Score** The subscales from the Depression, Anxiety, and Stress Scale (DASS-21) were used to assess symptoms of depression, anxiety, and stress (Henry & Crawford, 2005). Participants rated on a 4-point scale (0 = did not at all apply to me, 3 = applied to me very much, or most of the time) how much each statement applied to them over the past week. Scores for each subscale are summed and multiplied by 2 for

a final subscore. On the depression subscale, scores between 0 and 8 indicate normal/no depressive symptoms, 10 to 12 indicate mild depressive symptoms, 14 to 20 indicate moderate depressive symptoms, 22 to 26 indicate severe depressive symptoms, and 28 to 48 indicate extremely severe depressive symptoms. On the anxiety subscale, scores between 0 and 6 indicate normal/no anxiousness, 8 indicate mild anxiousness, 10 to 14 indicate moderate anxiousness, 16 to 18 indicate severe anxiousness, and 20 to 48 indicate extremely severe anxiousness. On the stress subscale, scores between 0 and 14 indicate normal levels of stress, 16 to 18 indicate mild stress, 20 to 24 indicate moderate stress, 26 to 32 indicate severe stress, and 34 to 48 indicate extremely severe stress.

Positive and Negative Affect Scale The Positive and Negative Affect Scale (PANAS)(Watson et al., 1988) uses a 5-point scale (1 = very slightly or not at all, 5 = extremely) to quantify whether participants identify with a particular emotion on average. The positive affect subscale (PANAS+) is assessed by questions 1, 3, 5, 9, 10, 12, 14, 16, 17, and 19, and the negative affect subscale (PANAS−) is assessed by questions 2, 4, 6, 7, 8, 11, 13, 15, 18, and 20. Scores are summed separately for PANAS+ and PANAS−, where higher scores indicate higher levels of each effect.

The Revised Life Orientation Test The Revised Life Orientation Test (LOT-R) asks participants to indicate the extent to which they agree with 10 different statements using a 5-point Likert scale (0 = strongly disagree, 4 = strongly agree) (Scheier et al., 1994). The optimism subscale of the LOT-R comprises the sum of questions 1, 4, and 10, where higher scores indicate higher levels of optimism.

Power calculation and sample size

The study is fully powered with 402 participants (Table 1). With a sample of 402 participants and assuming two-tailed type I error of alpha=.05, we have sufficient power (P>.8) to detect a small effect size (f2=0.02) with as many as 10 predictors included in the regression models.

Missing data

Five participants were removed from the sample as their pain catastrophizing scale questionnaires and ACE-IQ were not completed. Missingness was evaluated for total ACE-IQ scores (0%) and individual questions, ranging from 0.5% (physical neglect) to 5.2% (mental illness) (Table 2). Data was missing completely at random. Individual missing data, for example in individual ACE questions, were removed from analyses.

Analyses

All analyses were conducted in SPSS, version 27. Mediation analyses were conducted using PROCESS macro, v4 (Hayes, 2013). Descriptive statistics were to define the samples sociodemographic, clinical, and psychometric properties (Table 1). First, we explored the association between ACEs and demographic factors including sex, age and race. Given unequal N for each cell of the data, non-parametric analysis Mann-Whitney U test was used to determine the sex differences in ACEs. Kruskal-Wallis H tests were performed to explore the influences of race on ACEs. Wherever significance of the main effect was observed, post-hoc analyses were conducted applying Bonferroni correction for multiple comparisons.

Table 1, Sociodemographic, clinical, and psychological characteristics of participant sample, n=397

Sociodemographic Characteristic	**M [95% CI] or Frequency (%)**
Age	41.38 [39.98-42.77]
Sex	
Male	88 (22%)
Female	304 (76%)
Ethnicity	
Hispanic/Latino	366 (92.2%)
Non-Hispanic/Latino	21 (5.3%)
Unknown	10 (2.5%)
Race	
White	202 (50.9%)
African-American	138 (34.8%)
Mixed race	27 (6.8%)
American Indian/Alaskan Native	1 (.3%)
Education	
High school	47 (11.8%)
Some College	105 (26.4%)
Undergraduate degree	138 (34.8%)
Professional or postgraduate degree	107 (27%)
Clinical Characteristics	
Body Mass Index (BMI)	28.4 [27.69-29.11]
Pain duration, years	11.87 [10.81-12.93]
Psychological Questionnaire	M[95% CI] or Frequency (%)
GCPS-severity*	47.64 [45.45–49.83]
GCPS-interference*	
Pain Catastrophizing**	13.85 [12.73-14.97]
Rumination	5.47 [5.02-5.93]
Magnification	2.99 [2.71-3.27]
Helplessness	5.39 [4.90-5.88]
DASS***	
Depression	7.1 [6.26-7.93]
Anxiety	6.43 [5.74-7.12]
Stress	11.06 [10.25-11.87]
Optimism****	7.57 [7.33-7.81]
NEO-5 Extraversion*****	40.62 [39.95-41.29]
PANAS - Negative Affect******	19.59 [18.78-20.4]
PANAS - Positive Affect******	33.07 [32.25-33.89]

*** GCPS=Graded Chronic Pain Scale, **Pain Catastrophizing Scale, ***Depress Anxiety Stress Scale, ****Life Orientation Test, Revised, *****NEO Five Factor Inventory, ******Positive and Negative Affect Scale**

*Table 2, ACE-IQ Characteristics of the sample, n=397**

ACE scale or question	N (%)
ACE-IQ, Total Score, M (SD)	4.93 (2.8)
Household violence	266 (71.7%)
Emotional abuse	263 (71.3%)
Bullying	259 (69.6%)
Physical abuse	226 (61.7%)
Community violence	214 (57.5%)
Emotional abuse	263 (71.3%)
Mental illness	120 (33%)
Physical neglect	97 (25.5%)
Sexual abuse	84 (23.1%)
Alcohol/Drug use	77 (20.6%)
Incarcerated parents	54 (14.8%)
Emotional neglect	44 (11.7%)
Collective violence	41 (11%)

*Missing data: household violence: 12, bullying: 11, physical abuse: 17, community violence: 11, mental illness: 20, physical neglect: 2, sexual abuse: 19, alcohol/drug use: 10, incarcerated parents: 17, emotional neglect: 8, collective violence 9

Hierarchical linear regressions were used to test if ACE-IQ score significantly predicted chronic pain characteristics when controlling for age, sex, and race. The chronic characteristics were decomposed into pain intensity and pain interference. In each of the regression model, age, sex (man vs. woman) and race (White vs. non-White) entered in block one as covariates, and ACE-IQ score entered in block two as a predictor. GCPS chronic pain intensity and pain interference were set as dependent variables, separately. Linear regressions were also used to test the relationship between ACE-IQ subscales and GCPS score.

We examined the relationship between ACE score and pain threshold and pain tolerance using data obtained during quantitative sensory testing. ACE scores were categorized into no exposure (ACE-IQ=0), mild exposure (ACE-IQ=1-3), and severe exposure (ACE-IQ=4 and above). A univariate ANOVA was then conducted applying Bonferroni correction.

The chronic pain interference data was positively skewed (Skewness =0.85) with 134 out of 387 containing 0, causing a potential problem of zero-inflation. To address this, we dichotomized GCPS chronic pain interference into 1=having pain interference vs. 0=no pain interference. Logistic regressions were then conducted to determine whether early childhood adverse event exposure would have impacted the chronic pain interference in this cohort.

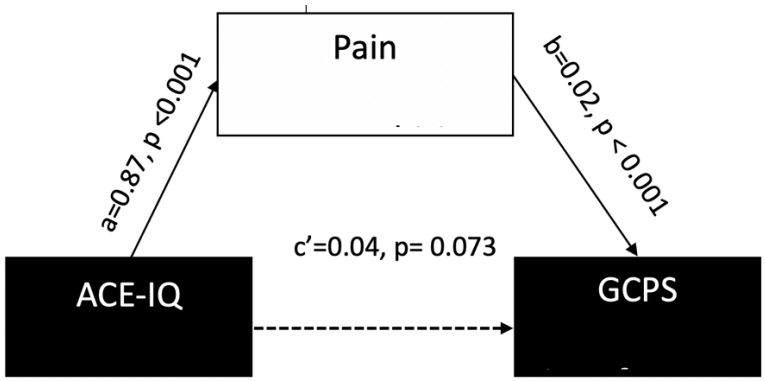
GCPS grade was examined as an integrative measurement of chronic pain intensity and interference. Given that GCPS grade was an ordinal variable, an ordinal regression model was estimated to investigate whether ACE score predicted GCPS grade.

Lastly, a mediation analysis was conducted to examine the effect of catastrophizing on pain in participants with adversity in childhood. In the mediation model, we designated ACE-IQ score as the independent variable and GCPS-interference as the dependent variable. Total PCS and its subscales were evaluated as potential mediators. Recent confirmatory factor analysis (CFA) determined that the subscales of the PCS (rumination, magnification, and helplessness) were valid (Cundiff-O'Sullivan et al., 2023). To determine the significance of the indirect effects (a*b), we used a bootstrap inference with 5000 iterations. Specifically, if the bootstrapped 95% confidence interval did not encompass 0,

the indirect effect was deemed as significant at the alpha level of 0.05. Age, sex, and race were treated as covariants in the mediation models.

The mediation model (Figure 2) was tested in a single model using a bootstrapping approach to assess the significance of the indirect effects at differing levels of the mediator (Hayes, 2013). ACE-IQ score was the predictor variable, with PC total score as the mediator. Additional analyses were conducted with PC subscales (rumination, magnification, and helplessness) as individual mediators. The outcome variable was GCPS grade. Mediation analyses, with bias-corrected 95% confidence intervals were used to test the significance of the mediated effects. This model explicitly tests the mediating effect on the predictor to mediator path. We accepted the IE as statistically significant only if its bias corrected 95% CI excluded zero.

Figure 2, Mediation model



Results

Demographic information and adverse childhood experiences Age was not correlated with the number of ACE categories (r=0.05, p=0.310). Men and women did not differ in number of ACEs categories (Man-Whitney U=11750.00, p=0.175). The significant main effect of race on number of ACEs (Kruskal-Wallis H=17.45, p=0.002) indicated that

mixed-race TMD participants reported more categories of ACEs than Asian ($p<0.001$), Black/African-American ($p=0.001$) and White participants ($p<0.001$).

ACEs and pain sensitization There was no significant correlation between ACE-IQ score, pain threshold and pain tolerance. A univariate ANOVA showed no main effects of ACE score on pain threshold or pain interference, suggesting ACE score does not influence pain sensitivity.

ACEs and chronic pain characteristics After controlling for age, sex, and race (White vs. Non-White), greater ACE-IQ scores predicted higher levels of chronic pain interference ($\beta=0.12$, $p=0.015$), but were not associated with chronic pain severity ($\beta=0.04$, $p=0.427$). We further looked at how ACE-IQ global scores were associated with the GCPS grade. The results of the ordinal regression indicated that ACE-IQ scores significantly predicted the GCPS grade (OR=1.10, $p=0.004$), suggesting that each point increase in ACE-IQ scores was associated with about 10% increase in the levels of GCPS grade.

Next, we investigated specific ACE categories and examined whether they were linked to the GCPS grade. TMD participants who had been exposed to early childhood sexual abuse were 84% more likely to have higher GCPS grade (OR=1.84, $p=0.008$). Moreover, physical neglect contributed to higher odds of more severe GCPS grade (OR=1.73, $p=0.012$). Other ACE categories were not significantly associated with the severity of chronic pain assessed by GCPS grade.

The mediating role of pain catastrophizing in the relationship between ACE and chronic pain The results from mediation analysis demonstrated a significant indirect effect of pain catastrophizing total scores in mediating the effects of ACEs on GCPS grade (a*b=0.02, BLCI=0.009, BUCI=0.371). Greater ACE-IQ was associated with higher levels

of PC (a=0.87, p<0.001), while greater PC was related to higher GCPS grade (b=0.02, p<0.001). The direct effect was not significant (c^1=0.04, p=0.073), suggesting that PC fully mediated this relationship.

When we tested each subscale of PC (rumination, magnification and helplessness), we found that all the three subscale significantly mediated influences of ACE on GCPS grade (rumination: a*b=0.01, BLCI=0.003, BUCI=0.262; magnification: a*b=0.01, BLCI=0.002, BUCI=0.233; helplessness: a*b=0.03, BLCI=0.012, BUCI=0.043). These findings indicated that PC and its individual psychological constructs were the driving force for higher severity of chronic pain.

Discussion

In the context of pain catastrophizing, Anderson et al. have suggested that magnification and rumination arise from a dysfunction in the primary appraisal stage, while helplessness arises from maladaptive secondary appraisal (Anderson & Hanrahan, 2008). Primary appraisal stage refers to the participants' anticipated potential harm, while secondary appraisal refers to the participants ability to cope with the same stressor (Fernandez De Henestrosa et al., 2023). In this study of professional dancers, Anderson *et al* found pain severity did not differ among participants, except when perceived as a threat, suggesting that pain catastrophizing behavior mediated pain severity (Anderson & Hanrahan, 2008). Our work validates this suggestion among participants with chronic orofacial pain who have experienced childhood trauma. Anderson's suggestion that catastrophization is the result of maladaptation in both the primary and secondary appraisal stages is particularly important to evaluating chronic pain after childhood adversity. Our analyses coupled with extant literature on how childhood trauma increases the use of pain

catastrophizing (MacDonald et al., 2021; Van Loey, Klein-Konig, et al., 2018; Vogel et al., 2019) and informs pain severity and modulation (Burke et al., 2017; Carlyle et al., 2021; Hauser et al., 2019; Krantz et al., 2019), suggests that survivors of childhood trauma are more likely to experience severe chronic pain.

Although we used PC as a mediator in our model based on recent literature suggesting it is a common coping mechanism in adult survivors of childhood trauma (Varallo et al., 2021), this mediation model relies on the theoretical foundation that pain catastrophizing is maladaptive. Given recent calls to reevaluate the concept of pain catastrophizing (Amtmann et al., 2018; Sullivan & Tripp, 2024), this mediation model may need to be re-estimated using additional covariates such as pessimism.

Lastly, further large-scale research is needed to determine a dose-response relationship between childhood adversity and chronic pain. For the analyses described in our study, a singular exposure to a specific trauma was classified as a positive exposure. The ACE-IQ does allow for further study of dose of trauma received through quantifying the amount of exposure the participant experienced. Additional analyses using dose of ACEs and chronic pain severity may help to establish a dose-response relationship.

Overall, the findings of our study indicate that adversity in childhood does significantly alter chronic pain severity in adulthood. In additional, we found that pain catastrophizing mediates this model. Given the difficulty, in treating pain when PC is present, our study indicates a need for further analgesic treatments aimed at addressing the complex physical and psychological needs of chronic pain patients with childhood adversity.

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Chapter 4: **The BRAVE Study: B**u**r**n Pain after **A**d**v**erse Childhood **E**xperiences: A mixed-methods pilot study of the experience of burn pain after childhood adversity

Abstract

The BRAVE Study: Burn Pain after Adverse Childhood Experiences is a mixed-methods study of the experience of burn pain after childhood adversity. This protocol utilizes the standard protocol items: recommendations for interventional trials (SPIRIT) framework to investigate the relationship between adverse childhood experiences (ACEs) score, as measured by the ACE-10, and the experience of burn pain in adulthood. Pain intensity and pain severity scores will be used to quantify acute burn pain. Semi-structured interviews and daily diaries will describe the individual experience of burn pain in survivors of childhood adversity. We hypothesize that patients with higher ACE scores will self-report higher pain severity and that there will be distinct differences in the qualitative experience of pain.

Keywords

Childhood adversity, pain, burn pain, ACEs

Background and rationale

Adverse childhood experiences (ACEs) impact over half of adults in the United States and are known to contribute to the development of a wide variety of negative health and behavioral outcomes (Jones et al., 2020). Originally defined by Felitti et al (1998), these experiences include events such as physical, mental, and sexual abuse, as well as neglect, divorce/separation, family incarceration, and violence, mental illness, or substance abuse in the home. There is emerging evidence that ACEs contribute to risks for chronic pain in both children and adults (Nelson et al., 2021; Salonsalmi et al., 2021) and are associated with increased severity of pain in medical conditions such as arthritis, back pain, and headaches (Sheinberg et al., 2019).

Findings of several lines of research have provided evidence that individual differences in pain responses and risks for chronic pain may be the result of trauma-induced alterations in the developing brain and in key neurobiological sub-states, such as the hypothalamic-pituitary-adrenal (HPA) axis, and autonomic and immune systems (Burke et al., 2017; Gupta et al., 2019; Salberg et al., 2021; Zouikr & Karshikoff, 2017). Moreover, maladaptive orientation toward actual or anticipated pain (Gatchel et al., 2007), such as pain catastrophizing (PC) (Sullivan et al., 2005) is linked to adversity in childhood. PC is strong predictor of disability in patients with chronic pain (Subramanian & Venkatesan, 2021; Varallo et al., 2021) and has been associated with several dimensions of the pain experience, including heightened affective responses (Varallo et al., 2021), increased pain severity (Kadimpati et al., 2015; Kanzawa-Lee et al., 2018), and longer duration (Brecht & Gatchel, 2019). Not surprisingly, given its links with affective responses to pain, PC is

also associated with depression and anxiety (Darnall & Colloca, 2018; Sturgeon et al., 2017) and may mediate relationships between psychological distress and pain experiences (Cassar et al., 2018; Pinto et al., 2012). While there has been only limited study of catastrophizing in burn patients, evidence of a relationship with pain sensitization and duration has been reported (Haythronthwaite et al., 2001). PC is known to predict chronic pain by 6 months post-injury(Van Loey, Klein-Konig, et al., 2018). This suggests that screening for a history of child maltreatment and tendency to catastrophize could lead to early identification of individuals who are at greater risk of developing chronic pain following a burn injury. As patients with chronic pain are at higher risk of opioid use disorder (OUD) it stands to reason that early identification of chronic pain risk could also help identify individuals at risk of OUD. To date, the effect of catastrophizing on acute burn pain has not been explored in burn patients with ACEs.

ACEs are an emerging concern in burn patients, who account for almost 450,000 hospitalizations in the United States annually (Association, 2021). Anecdotal evidence suggests that up to 40% of the adult burn population has had ACE exposure (Fassel et al., 2019). Yet, despite evidence that ACE exposure worsens pain outcomes in patients with other kinds of pain, only one published study has specifically explored the relationship between ACEs and burn injuries (Fassel et al., 2019). Although the pathophysiology of acute burn pain is not yet fully understood, available data indicate that the mechanisms involve both peripheral and central processes and activation of nociceptive, neuropathic, and inflammatory pain pathways (Haddock et al., 2010; Kim et al., 2019; Klifto et al., 2020; Morgan, Deuis, Frosig-Jorgensen, et al., 2018; Retrouvey et al., 2020). Based on a review of the literature, we propose the investigating the impact of ACEs on adult, acute

burn pain survivors during their initial inpatient hospitalization. We propose using patient reported pain at multiple time frames during routine wound care procedures and in their recovery after discharge to assess the pain experience.

Objectives

The objective of the study is to determine how ACEs influence burn pain intensity and opioid requirements using a mixed methods approach. The primary hypothesis is that there will be distinct qualitative themes differentiating the burn pain experience between no, moderate, and high ACE score participants. The secondary hypothesis is that the intake of morphine equivalent dose (MED) will be higher in participants with moderate and high ACE exposure than those with no ACE exposure. The tertiary hypothesis is that PROMIS pain intensity scores will be higher at baseline and during wound care procedures for moderate and high ACE participants than those with no ACE with a moderating effect of PC.

Study setting & eligibility requirements

The study will be conducted at the Johns Hopkins Burn Center (JHBC), a large, regional burn center. The JHBC is an American Burn Association (ABA) verified burn center serving over 800 adults annually. The JHBC is also home to multiple research studies including industry sponsored clinical trials. Eligibility requirements include age over 18 years and an admitting diagnosis of an acute burn, burn related injury, or disease process treated in a burn center. Participants must also report pain of at least 3/10 within 24 hours of their enrollment and be expected to remain hospitalized for at least 5 days from the time of enrollment. Exclusion criteria include inability to consent, pregnancy, incarceration, and/or active psychosis. Patients with schizoaffective disorder, major

depressive disorder, and generalized anxiety disorder may be excluded if their diagnosis prevents their ability to participate in the tools and interviews utilized in this study.

Procedures

Upon enrollment, participants will complete the ACE-10 survey. Three groups of participants will be grouped according to their ACE score using the cut-off scores of 0 (no exposure) 1-3 (moderate exposure) and 4-10 (high exposure) established by Hughes et al (Hughes et al., 2017). A convenience sample of the first five participants with ACE scores greater than four will be used to create the high ACE sample. A convenience sample of the first five participants with ACE scores of 0-3 will be used to create the low ACE group. A convenience sample of the first five participants with ACE scores of 0 will be used to create the no ACE sample. Together, they will create the total sample of 15 participants. A convenience sample of the first three participants from each group will be selected to complete recorded diaries. At any time, participants may withdraw from the study. Participants who demonstrate significant emotional distress during semi-structured interviews and/or inability to complete recorded diaries may be removed from the study pending evaluation from the inpatient burn psychologist.

PROMIS pain intensity scores will be obtained 30 minutes prior to scheduled wound care sessions and at 15-minute increments during wound care sessions. In order to provide consistency among sessions, wound care sessions that include post-operative take downs or staple removal will be excluded. During wound care sessions all regularly scheduled, titratable, and as needed medications will be available to participants. Pre-medications, if applicable, will be given at the time of the 30-minute pre-intervention

PROMIS pain intensity score. The primary outcome is the change in baseline PROMIS pain intensity for each group of participants. The secondary outcome is MED.

Qualitative data will be collected using semi-structured interviews and self-recorded diaries is a subgroup of each sample. Diary entries will be recorded on day of enrollment, days of wound care, and days of the semi-structured interviews.

Participant timeline

Participants will remain enrolled in the study for the duration of their inpatient stay. As such, the timeline is dependent upon their injury and plan of care. In general, it is estimated that the length of stay is one day per percent body surface area burn.

Sample size

We propose a sample of 15 participants for qualitative data collection, using Guest's suggestion of a minimum of 12 participants (Guest et al., 2016). Nine of these participants will also be recruited for quantitative data collection. We plan to enroll 16 participants, with an expected dropout rate of approximately 5%, to obtain a sample of 15. Five participants will be enrolled in each group: no ACE, moderate ACE, and high ACE. A convenience sample of nine participants will participate in self-recorded diary entries to explore the qualitative portion of aim three.

Recruitment

15 participants will be recruited by the on-site principal investigator. A pilot study was able to successfully enroll 12 participants with more stringent enrollment criteria. A daily screening of newly admitted patients will be completed by the PI or designated study team member. Participants will be recruited using the IRB approved study introduction letter and direct recruitment of patients admitted to the burn center.

Methods

Data collection methods

We will use the ACE-10 tool to assess childhood adversity. Originally designed for use in the United States, the tool is well suited to the proposed population. The ACE tool is a simple screening tool of 10 yes or no questions that inventories exposure to neglect, physical abuse, sexual abuse, and instability in the household(Felitti et al., 1998). Each yes response earns an additional point. A score of zero indicates no exposure to childhood adversity, while a score of ten indicates significant adversity in childhood. The ACE tool will be used to assign a score to each participant. The ACE tool will provide the basis for assigning participants to the appropriate group.

The PROMIS pain severity tool will be used to assess pain(Cella et al., 2010). The pain catastrophizing scale will be used to measure all three subscales of pain catastrophizing (Darnall et al., 2017). The pain disability index score(Pollard, 1984) will be used in conjunction with collection of comorbidity data to control for preexisting pain disorders. Barth's expectations for treatment(Barth et al., 2019) will be used to measure participants' individual expectation of pain relief in each wound care session. Daily opioid use for all participants will be standardized using the morphine equivalent dose (MED) to control for variations in medication, route, and dosage.

Qualitative research with selected participants will describe each participant's ACE exposure. Participants will be asked to describe patterns of frequency, duration, and significance of childhood adversity through prompts for oral diaries.

Burn patients with ACE exposure also represent an opportunity to investigate the impact of negative patient expectations of pain on the effectiveness of pain management.

Previous research into the impact of expectations on placebo and nocebo has demonstrated that patient expectations, particularly related to prior hypoalgesia, impact pain relief (Luana Colloca et al., 2020). Further research in this area indicates that negative expectations and catastrophizing increase central sensitization, decrease effectiveness of pharmacologic analgesia, and contribute to the development of chronic pain (Darnall & Colloca, 2018). A Visual Analog Scale will be used to measure expectations from 0=no expectation of pain relief to 100=maximum expectation of pain relief as previously done (L. Colloca et al., 2020). Previous research also links catastrophizing as a coping mechanism for adult ACE survivors (MacDonald et al., 2021).

Table 3, Quantitative tools used in the BRAVE Study

Measure	**Concept Measured**	**Scale**
ACE-10	childhood adversity	0-10
Pain Catastrophizing Scale	impact of catastrophizing on pain severity	0-52
PROMIS Pain Intensity	acute pain	1-5
Expectation of Treatment Scale (ETS)	expectations about coping ability, vitality, physical health and reduction of patient complaints	5-20
PROMIS pain interference	Impact of pain on physical, mental, social activities	6-30
Pain Disability Index	impact of pain on disability	0-50
Morphine Equivalent Dose (MED)	Daily opioid use	Continuous

Data management

Protected health information (PHI) collected will be stored in REDCAP. Access will be limited to the principal investigator and one additional study team member. The additional study team member will be responsible for double data entry, range checks, and validation of qualitative themes. REDCAP files exported for statistical analysis will be

conducted in SPSS 27 on the HIPAA compliant SAFE desktop. Self-recorded audio files and field notes will be stored in the locked, single occupancy office of the PI. Transcription will occur in HIPAA compliant qualitative software program. A data monitoring committee is not required for this study due to its size and type of data being collected.

Statistical methods

All statistical analyses will be conducted in SPSS 27. Demographic information including descriptors of the burn injury will be used to describe the samples. The outcome variables are pain intensity and MED. Potential confounders including mental health diagnoses, chronic pain, substance use disorders, comorbidities, extent of burn injury, and depth of burn injury will be controlled for in statistical analyses. Sex is known to affect the experience of pain(Yamada et al., 2017). Care will be taken to recruit equal numbers of men and women in the sample. Statistical analyses will control for age, sex and race.

Quantitative and qualitative data will be mixed. Quantitative data will be analyzed using multiple linear regressions to analyze the relationship between pain intensity, opioid use, and ACES. Ordinal and logistic regressions will also be used with ordinal level data to examine the relationship between the subscales of pain catastrophizing and the ACE-10 tool. Colaizzi's descriptive phenomenological method will be used for data analysis of interview transcripts. The method includes seven steps: familiarization, identifying significant statements, formulating meaning, grouping themes, creating the exhaustive description, creating the fundamental structure of the phenomenon, and, finally, verifying the structure of the phenomenon (Colaizzi, 1978). Familiarization will occur through transcription of the audio recording of the interview. Significant statements will be identified that are relevant to the experience of burn pain after ACEs. Attempts to bracket

personal experience from interfering with the construction of meaning from the significant statements will be made. The interview guide pilot tested in the burn center will be used as the basis for diary prompts. Prompts will be reviewed throughout the study when new themes are discovered. In vivo codes will be developed in the initial analysis of the interview transcript. Two members of the study team will independently code transcripts. Themes will also be confirmed after collection with participants. Qualitative themes will be quantized to determine commonalities of the pain experience. Quantitative data will be qualified using common themes across and within groups to describe pain. This data mixing plan strengthens the qualitative and quantitative data, thereby creating a fuller understanding of the phenomenon.

Monitoring

Although the study is low risk there are small risks including loss of confidentiality and emotional distress while participating in surveys. Confidentiality risks will be addressed through secure storage of data in HIPAA compliant software, as well as in a locked single-occupancy office. Participants will be assigned study record numbers to further anonymize their responses. The dedicated burn unit psychologist is available for consult for any emotional distress associated with the surveys. In the event of psychiatric emergencies, on-call psychiatry is available at all times. Any harms will be reported to the IRB in accordance with its established procedures.

Ethics and dissemination

We will obtain approval from the Johns Hopkins Health System IRB. Protocol modifications will be communicated in writing to the IRB per established protocols. Informed consent will be obtained from all participants. Supplementary consent will be

obtained from participants willing to participate in future studies. Biological specimens will not be collected. Participant data will be stored using study record number as the sole identifier in HIPAA compliant software. IRB logs will be stored in a locked-single occupancy office. Access to data will be limited to the PI and one study team member only. Given the nature of qualitative data obtained and potential for loss of confidentiality given the small sample size, the final dataset will not be made available. There are no financial or competing interests for any study team members.

Results of the study will be disseminated through presentation at regional, national, and international conferences. Results will also be disseminated through publication. The full protocol will be made available upon request.

Anticipated results

Given previous lines of research that demonstrate increased severity of pain in ACE survivors with pelvic pain (Krantz et al., 2019), chronic pain (Dennis et al., 2019), and gastrointestinal pain (Sherman et al., 2015) we expect that participants with higher ACE scores will have higher pain intensity and interference than participants with no ACE exposure or moderate ACE exposure. We further hypothesize that chronic pain participants with high ACE scores will experience higher levels of pain catastrophizing than those with no or moderate ACE exposure. Importantly, we anticipate this catastrophizing will also inform distinct qualitative differences in the experience of pain to be identified in semi-structured interviews. We further anticipate that participants with high ACE scores will require higher MED during routine wound care than those with no or moderate ACE exposure. Lastly, we anticipate that PROMIS pain intensity and VAS pain severity scores will be higher for moderate and high ACE participants than those with no ACE exposure.

A significant strength of the study is the collection of qualitative data. We expect this qualitative data to inform the quantitative data, allowing for the full story of how ACE exposure changes the experience of pain in adulthood to be told.

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Chapter 5: The Lasting Legacy of Adversity in Childhood

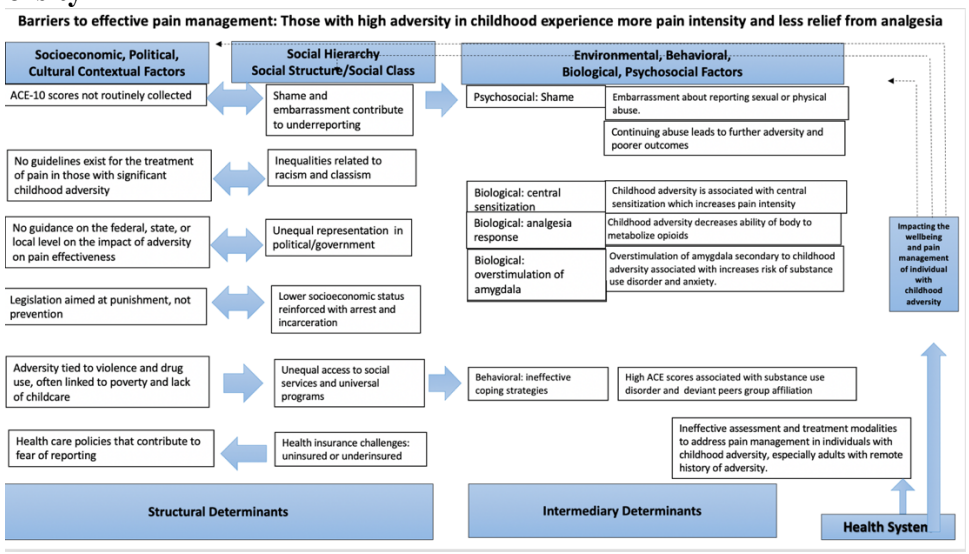
Introduction

As explored in prior chapters, childhood trauma plays an important role in worsening pain secondary to increased stress response and pain catastrophizing (You & Meagher, 2016, Sheinberg et al., 2019; Van Loey et al., 2018). Adults with ACEs often find their pain unmanaged or mismanaged secondary to the biological, psychological, and social changes that adversity in childhood causes. When combined, the effects of these multi-dimensional changes result in pain that is more severe (Hughes et al., 2017), less receptive to traditional narcotic medication (Merrick et al., 2020), and more likely to result in tolerance, dependence and substance use disorder (SUD) (Khoury et al., 2010).

Eventually, these sequalae contribute to the self-fulfilling prophecy wherein the adult survivor of childhood adversity develops chronic pain or substance use disorders, often limiting opportunity for occupational and financial advancement(Frederick & Goddard, 2007; Liu et al., 2013). The development of ACES themselves are, however, linked to structural determinants of health including government assistance programs (Chilton et al., 2015) and drug legislation that leads to mass incarceration of racial and ethnic minorities (Ashekun et al., 2023). These structural determinants directly impact intermediary determinants of health including specific biological, psychological, and social changes that survivors of ACEs experience. Adult survivors of ACEs, especially those with pain conditions, become consumers of the health care system that then perpetuates stereotypes that negatively impacts their care (Gjelsvik et al., 2014; Hargreaves et al., 2019). The final chapter of this dissertation will explore the dynamic

relationship between adult survivors of ACEs, their pain and the structural and intermediary determinants of health that impact survivors and the health care system (Figure 3).

Figure 3, Barriers to effective pain management in survivors of childhood adversity



Structural determinants

Although many structural determinants play a role in establishing and maintaining environments that allow ACEs to continue, public policy plays the largest role. In addition to public policy that address government assistance programs, socioeconomic status and social hierarchy influence the development of ACEs by reinforcing underreporting of child abuse/neglect and unequal access to early intervention programs (Barnard-Brak et al., 2021). Without addressing these key determinants of health, the 60 million Americans experiencing ACEs will continue to increase (Adverse Childhood Experiences, 2021). Importantly for the purposes of this paper, the sequalae of ACE exposure will also continue to increase and put millions at risk for mismanagement and chronicization of pain.

Lower socioeconomic status is associated with an increased risk of ACE exposure (Walsh et al., 2019). Poverty fundamentally alters cognitive processing by changing the

structure of the brain's gray matter, causing cognitive changes and increased risk of toxic stress that does not dissipate with adulthood (Short, 2019). While the science is clear that low socioeconomic status is associated with increased risk of food scarcity, housing insecurity, and domestic violence, public policy to address poverty in the United States has largely failed (Orloff, 2002). It is interesting to note that much of the literature in social work and public policy on the subject of childhood poverty was completed in the late 1990s/early 2000s following the 1996 welfare reform act and the publication of Barbara Ehrenreich's seminal work, *Nickel and Dimed*. Since the 1996 welfare reform act, government assistance programs including WIC, SNAP, and housing vouchers have continued to decline, offering fewer benefits to those who need it most (Orloff, 2002). The failure of public policy to address childhood poverty undermines efforts to limit exposure to ACEs (Bignall, 2021) and solidifies multi-generational poverty by limiting the possibility of building wealth.

Public policy, in the form of drug legislation, also increases the likelihood that children of color will experience ACEs as one of the domains that contributes to an overall ACE score is the incarceration of a family member(Gjelsvik et al., 2014; Zhang & Monnat, 2022). With increased policing in low-income neighborhoods, criminalization of marijuana possession and other "tough on crime" initiatives of the 1990s and early 2000s, children of color disproportionately experienced the incarceration of family members (Giano et al., 2020; Tucker, 2017), increasing their ACE dose. Moreover, as children with ACEs become adults who are more likely to develop substance use disorders (Khoury et al., 2010), public policy aimed at incarcerating adult drug users after hard-wiring their brains for substance use in childhood is particularly troublesome.

The combination of decreasing government assistance programs and increasing parental incarceration has served to increase the childhood trauma of generations of Americans, particularly those of color. For the purposes of this discussion, it is important to note that ACEs disproportionately affect the poor and people of color (POC) (Giano et al., 2020). POCs are also more likely to have their pain under assessed and under managed (Morden et al., 2021), leading to extended periods acute pain. Undertreated pain is correlated with further increased risk of substance use disorder, chronic pain, and depression(van Ransbeeck et al., 2018). As adult survivors of ACEs may experience pain more severely(McCall-Hosenfeld et al., 2014; Pieritz et al., 2015), their risk for the serious sequalae of untreated pain is compounded by structural determinants of health, especially for people of color. The lack of affordable, universal health care also contributes to the structural determinants domain as it prevents ACE survivors from accessing quality health care (Institute of Medicine Committee on Advancing Pain Research & Education, 2011).

Intermediary determinants

Just as mass incarceration and limitations in government assistance programs perpetuate childhood adversity structurally, the central sensitization (You et al., 2019) and epigenetic changes associated with ACEs continue the cycle of adversity through multiple generations (Lessans & Dorsey, 2013). Central sensitization is the result of repeated, prolonged stress associated with child abuse and neglect (You & Meagher, 2016). In the long term, the repeated insults to the central nervous system result in heightened pain sensitivity, increased pain intensity, and decreased response to opioid medications (You & Meagher, 2016). Toxic stress also causes repeated insults to the amygdala, resulting in structural changes to the brain (Herringa et al., 2016). The prolonged stress associated with

childhood adversity also leads to epigenetic changes. In particular, the methylation of FKBP5 (Lang et al., 2020) and TRPA1 (Achenbach et al., 2019) genes increase aggressive behavior, risk of substance use disorder, risk of development of chronic pain, and depression. Individual epigenetic changes are not, however, limited to the individual. These epigenetic changes are passed to children, producing intergenerational trauma responses. As a result, these inherited epigenetic responses to trauma become inherited intermediary determinants that increase the risk of development of chronic illness and pain for generations of families exposed to trauma.

Psychosocial and behavioral changes in ACE survivors are also intermediary determinants that increase the risk of unmanaged pain in this population. Ineffective coping strategies such as catastrophizing (Brecht & Gatchel, 2019) and affiliation with a deviant peer group (Yang et al., 2021) often reinforce maladaptive behaviors. The shame associated with childhood adversity is also known to contribute to the adaptation of ineffective coping strategies (Yang et al., 2021), including catastrophizing.

Health system

The individual and societal impact of ACEs on the health care system is profound. As previously discussed, ACEs predispose adults to the development of difficult to manage, severe pain and the development of substance use disorder (Bussieres et al., 2020). In combination, pain and substance use disorders create tremendous stress on the health care system. However, the reverse is also true. The ways in which pain and SUDs are assessed and treated in the health care system often contribute to societal stigma surrounding both disorders.

In the United States pain impacts over 50 million Americans, 20 of whom have what is termed “high impact” pain, requiring frequent intervention and assessment (Dahlhamer J, 2016). With the rise of patient reports assessment tools such as PROMIS, much progress has been made in the way pain is assessed clinically (Deyo et al., 2016). However, much work remains to be done when assessing pain in patients with trauma history. The foundational principle of trauma informed care is that the provider should acknowledge and understand the trauma (Purkey, 2018). Without universal screening for ACEs this principle cannot be applied with any meaningful regularity.

Instead, ACE survivors with pain are often labeled are drug seekers, frequent fliers, with their complaints dismissed (Merrill, 2002). The lack of trust between those with pain and providers is mutual (Merrill, 2002), with both groups assuming the other is engaging in dishonest communication and judgement. The result is under assessment of pain and undertreatment of pain (Merrill, 2002). This non-patient centered care approach to pain management is further complicated by systemic racism inherent in the health care system and the United States. It has been well established that POCs complaints of pain are often under-triaged secondary to health care providers belief in racial differences that make Black patients better able to manage pain without medication (Hoffman et al., 2016). In fact, in a large retrospective study researchers found that on average Black Americans received medication dosages 36% lower than their white counterparts (Morden et al., 2021).

On the individual level, the impact of mistrust in the health care system results in millions of Americans delaying seeking care (Hoffman et al., 2016). From a health systems perspective, this results in increased cost to the system, insurance companies, and

individuals. On the individual level, one study recently reported that patients with chronic pain spend on average $7,726 more per year than those without pain (Gaskin & Richard, 2012). When combined with lost productivity, medical treatments and disability payments, pain costs the already overtaxed United States health care system over $600 billion per year (Institute of Medicine Committee on Advancing Pain Research & Education, 2011).

Conclusion

The development of ACEs in the United States is in part the result of a failure of structural determinants of health including welfare and drug policy. Additional intermediary determinants including the biological and epigenetic changes associated with ACE exposure contribute both to the intergenerational trauma load and the individual experience of ACEs. In the large number of adult survivors of ACEs who develop pain in adulthood, these structures reinforce mistrust of the health care system, leading to often dysfunctional treatment options.

Given the prevalence of ACEs and well-embedded structural determinants that impact the development of pain in this population, there is much advocacy work to be done. First and foremost, health care providers must begin assessing the trauma load of their patients either through the ACE-10 tool or the lifetime trauma inventory tool. Second, advocacy work to reduce the impact of ACEs by way of early intervention must be robust. Last, and perhaps most important, health care workers must continue to educate and advocate on behalf of the adult survivors of ACEs. The call to action for children of abuse is strong. It is now time for health care workers to advocate for the adults who continue to live with the legacy of their childhood adversity.

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