Perceived injustice and opioid use problems among patients with chronic pain: The contribution of daily pain intensity, negative affect, and catastrophic thinking

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Abstract

Background: Over the past two decades, the rise in the use of opioids has been accompanied by high rates of prescription opioid misuse among patients with chronic pain. Opioid craving has emerged as a robust determinant of opioid misuse, but the factors that contribute to opioid craving have yet to be fully elucidated. Perceived injustice is a factor observed among patients with chronic pain that could contribute to opioid craving. Perceived injustice has been linked to numerous negative pain outcomes, but its association with craving and opioid misuse has yet to be examined.

Objectives: The first objective of this thesis was to examine the association between perceived injustice and opioid misuse in patients with chronic pain who are prescribed opioids. The second objective of the thesis was to examine the association between perceived injustice and opioid craving. Lastly, pain intensity, negative affect, and catastrophizing were examined as potential mediators of the relationship between injustice and opioid craving.

Methods: In this longitudinal study, patients with chronic noncancer pain (n = 103) prescribed opioids completed baseline questionnaires assessing a host of demographic, clinical, and psychological variables, including perceived injustice. Patients then completed daily measures of pain intensity, negative affect, catastrophizing, and opioid craving for 14 consecutive days. At the end of the diary period (i.e., day 14), patients completed a measure of opioid misuse.

Results: Results indicated that perceived injustice was not significantly associated with any type of opioid misuse behaviour. However, analyses revealed a significant association between perceived injustice and opioid craving ($p < .01$), with higher levels of perceived injustice being associated with heightened levels of opioid craving. Higher levels of perceived injustice were also associated with greater daily levels of pain, negative affect, and catastrophizing (all p's $< .05$). A

multilevel mediation analysis indicated that the association between perceived injustice and craving was significantly mediated by catastrophizing ($p < .05$).

Conclusions: Findings from the present thesis provide new insights into the potentially negative impact of perceived injustice among patients with chronic pain. In addition to contributing to the higher daily levels of pain and negative affect, our findings suggest that high levels of perceived injustice are also associated with heightened levels of opioid craving, a variable known to be associated with opioid misuse in patients with pain. Specifically, findings from our mediation analysis suggest that higher levels of perceived injustice are associated with heightened daily levels of catastrophizing, which in turn could lead to heightened levels of opioid craving. These findings could have implications for clinicians involved in the management of patients with chronic pain who are prescribed opioid therapy. Our findings could also have implications for future interventions aimed at minimizing prescription opioid misuse in patients with chronic pain.

Résumé

Contexte: L'augmentation de l'usage d'opioïdes a été accompagné par des taux élevés de mésusage d'opioïdes. Les désirs et envies d'utiliser des opioïdes (i.e., *craving*) ont émergé comme un déterminant robuste du mésusage d'opioïdes, mais les facteurs contribuant au désirs/envies d'utiliser des opioïdes n'ont pas encore été élucidés. L'injustice perçue est un facteur ayant été observé chez les patients en douleur chronique qui pourrait contribuer aux désirs/envies liées aux opioïdes. L'injustice perçue a été liées à plusieurs problèmes reliés à la douleur, mais son association avec les désirs/envies d'usage d'opioïdes et le mésusage d'opioïde n'a pas encore été étudié.

Objectifs: Le premier objectif de cette thèse était d'examiner l'association entre l'injustice perçue et le mésusage d'opioïdes chez les patients en douleur chronique étant prescrit des opioïdes. Le deuxième objectif de la thèse était d'examiner l'association entre l'injustice perçue et les désirs/envies liées aux opioïdes. Finalement, l'intensité de la douleur, l'affect négatif, et la pensée catastrophique ont été examinées comme variables médiatrices de la relation entre l'injustice perçue et les désirs/envies liées aux opioïdes.

Méthodes: Dans cette étude longitudinale, des patients avec douleur chronique non-cancéreuse (n = 103) étant prescrits des opioïdes ont complété des questionnaires lors d'une visite initiale visant à mesurer des variables démographiques, cliniques, et psychologiques. Les patients ont ensuite complété des mesures quotidiennes d'intensité de douleur, d'affect négatif, de pensée catastrophique, et des désirs/envies liées aux opioïdes, pendant 14 jours consécutifs. À la fin de ces 14 journées, les patients ont complété une mesure visant à évaluer le mésusage d'opioïdes.

Résultats: Les résultats ont indiqué que l'injustice perçue n'est pas significativement associée à aucun type de comportement de mésusage d'opioïdes. Cependant, les analyses ont révélé une

association significative entre l'injustice perçue et les désirs/envies liées aux opioïdes ($p < .01$), alors que des niveaux plus élevés d'injustice perçue ont été associés avec des désirs/envies plus élevées envers les opioïdes. Des niveaux plus élevés d'injustice perçue ont aussi été associés avec des niveaux quotidiens plus élevés de douleur, d'affect négatif, et de pensée catastrophique (tous $p < .05$). Une analyse multiniveau a indiqué que l'association entre l'injustice perçue et les désirs/envies liées aux opioïdes est expliquée (i.e., médiée) par la pensée catastrophique ($p < .05$). **Conclusions:** Les résultats de la présente thèse fournissent des perspectives nouvelles par rapport à l'impact négatif de l'injustice perçue chez les patients en douleur chronique. En plus de contribuer à des niveaux plus élevés de douleur et d'affect négatif, nos résultats suggèrent que des niveaux élevés d'injustice perçue sont aussi associés à des désirs/envies plus élevées envers les opioïdes, qui sont connus pour être associés au mésusage d'opioïdes. Plus spécifiquement, les résultats de notre analyse de médiation suggèrent que des niveaux élevés d'injustice perçue sont associés avec des niveaux quotidiens plus élevés de pensée catastrophique qui, en retour, mènent à des désirs/envies plus élevées envers les opioïdes. Nos résultats pourraient avoir des implications pour les cliniciens impliqués dans la gestion de la douleur de patients étant prescrits des opioïdes. Nos résultats pourraient aussi avoir des implications pour les interventions futures visant à minimiser le mésusage d'opioïdes chez les patients en douleur chronique.

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Contribution of Authors

The supervisor (Dr. Martel) and the MSc candidate (Ms. Verner) jointly contributed to the methodological design of the study included in the present thesis. Ms. Verner conducted the literature search and contributed to the collection of study data. All study analyses were also conducted by Ms. Verner under Dr. Martel's guidance. Ms. Verner led data interpretation efforts, prepared all study figures, and wrote all parts of the initial version of the present thesis. The supervisor (Dr. Martel) provided feedback on the outline and initial version of the thesis.

1.0. Introduction

1.1. Pain

As of July 2020, pain is defined as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" by the International Association for the Study of Pain (IASP). However, arriving to this definition, which may change again in the future as we continue to learn about pain, has been a very long journey that started four centuries ago.

Pain is usually described anatomically by the location of the pain, the organ affected, or the cause of pain onset. Pain can be nociceptive (pain from tissue damage), neuropathic (pain from lesion or disease of the somatosensory nervous system), or idiopathic (pain of unknown origin) [84].

Time is a component that differentiates acute pain from chronic pain. Acute pain has been defined as pain lasting for less than three months [192], although many consider acute pain to last up to six months [192]. Acute pain can be caused by diseases, medical procedures, or trauma. Acute pain is generally assumed to serve a protective function by signaling actual or potential tissue damage [137]. However, lengthy exposure to acute pain and nociceptive input may causes lasting changes in the nervous system, which in turn may contribute to pain chronification [137].

When pain persists long past the accepted healing time, generally three or six months after the initial injury, pain is considered to be chronic [192]. Whereas acute pain is evolutionarily adapted to warn us of injuries, chronic pain is seen as a maladaptive process [137, 168]. The prevalence of chronic pain is quite high, with 20–30% of the Canadian population suffering from it [155]. It affects women more than men and its prevalence increases with age [155]. The areas most commonly affected are the lower and upper back, knees, legs, shoulders, neck, hips and head [155].

1.2. Historical perspectives on pain

The roots for the current model for pain perception can be traced back to René Descartes, a French philosopher from the 17th century [178]. Descartes described pain as a purely biological phenomenon: a painful stimulus would cause pores to open and send "animal spirits" through hollow tubes and open a valve in the brain that would alert the person to the painful stimulus [178]. The biological approach to pain was revolutionary in its time [178]. Whereas previously pain was a mysterious phenomenon at the whims of divine powers, Descartes proposed a plausible pathway and mechanism through which pain could be acting. In addition to firmly cementing pain as a biological phenomenon, Descartes proposed that the brain had a role to play in the pain experience [178]. However, in 17th century Europe, the brain and the mind were considered entirely separate entities. The brain was believed to be an organ fulfilling a function, but the mind was considered part of one's immortal soul and would be carried on into the afterlife. Descartes' biological approach to pain and lack of consideration for the mind's role led him to overlook important aspects of pain perception such as its unpleasantness, social implications, and what responses it may elicit. Descartes' dualistic perception of the mind and body endures in the attitudes of some healthcare professionals, but new models of pain have since emerged that take a more holistic approach.

In 1965, three centuries after Descartes' model, Melzack and Wall [128] proposed the Gate Control Theory (GCT) of pain. According to this theory, pain sensations are transmitted via afferent neurons and modulated by a "gating" mechanism in the spine, through the substantia gelatinosa [128]. It was also suggested that the gating mechanism could be influenced by ascending pathways (i.e., mechanoreceptors) or through descending pathways (i.e., the brain) [128]. This gating mechanism could either facilitate the transmission of pain signals to the brain or inhibit them [128].

By including a descending pathway, Melzack and Wall proposed that much more than biology was at play: emotional and cognitive processes also determined the pain experience [128]. This led to a major shift in the way people thought about pain [178]. Pain was no longer considered to be an exclusively biological phenomenon, as it included important psychological processes as well. Consequently, changes were made in how pain was researched, assessed, and treated [127, 178, 200].

After the GCT made a breakthrough for pain research and treatment, another theory emerged that built upon the importance of psychological and social factors. The biopsychosocial model of pain was developed in 1980 by John D Loeser [105]. This model proposed that pain is influenced by three kinds of factors: biological, psychological, and social [71, 105]. The biological and psychological aspects of pain had been established. However, the social aspect of pain was a relatively new avenue of research. Individuals have a bi-directional relationship with their environment, whereby they affect their surroundings, and their surroundings affect them. This is equally true when someone experiences pain [105]. When someone gets injured and feels pain, they can express this in several ways: they may shout out in pain, grimace, or cry. These are social signals that the person is in pain and needs help and are referred to as "pain behaviours" [77, 120]. Pain behaviours affect pain perception itself and other pain outcomes such as disability [86, 105]. Furthermore, the way that people around react to the pain behaviour also has an impact on pain outcomes [87]. Although the expression of pain behaviours may trigger empathy [74, 77, 119], research has shown that pain behaviours also have the potential to elicit negative personality trait inferences [120-122], as patients expressing certain types of pain behaviours may be viewed as faking [121], less likable [39, 122], or less dependable [122]. The biopsychosocial model acknowledges the importance of contextual cues such as pain behaviours and interweaves biological, psychological, and social factors of the individual experiencing pain for understanding pain [105].

1.3. The role of psychological factors in chronic pain

The biopsychosocial model of pain has played a key role in bringing greater attention to the role of psychological factors in the experience of chronic pain [71]. It is now well recognized that a wide range of cognitive and emotional processes may contribute to shaping pain perception and patients' adjustment to chronic pain [53] [199]. Over the past few decades, hundreds of studies have shown that patients presenting with high levels of anxiety or depressive symptoms (i.e., negative affect) tend to report higher levels of pain (for reviews, see [52, 92, 95]). Catastrophic thinking, a negative and pessimistic orientation towards pain, has also been consistently associated with negative pain-related outcomes [51, 182]. Patients with high levels of catastrophizing have a tendency to ruminate about pain, to magnify the threat value of pain sensations, and feel helpless when experiencing pain [182, 186, 187]. Higher levels of catastrophizing have been associated with higher levels of pain, greater levels of emotional distress, and greater functional disability among patients with various types of chronic pain conditions (for reviews, see [51, 182]). Several other psychological factors have also been found to influence pain-related outcomes among patients with chronic pain, including self-efficacy beliefs [89, 94], pain-related fears [5, 206], coping [90, 93], and pain acceptance [123, 124].

1.4. Interventions for the management of patients with chronic pain

Despite advances in our understanding of pain mechanisms, chronic pain remains challenging for patients and clinicians. As such, the complete cure of chronic pain is close to impossible and rarely established as treatment objective, with most physicians aiming to help patients manage their pain [106, 202]. Interventions for chronic pain are usually offered through primary care (i.e., family doctors) or tertiary care (e.g., pain specialists). The management of pain in tertiary care usually involves multidisciplinary pain clinics that includes healthcare

professionals from a wide range of disciplines. Some of the interventions that are commonly used for the management of chronic pain include interventional treatments (e.g., surgery, implantable devices, injections) as well as physiotherapy. Psychological interventions such as cognitive-behavioural therapy (CBT) and acceptance and commitment therapy (ACT) are also commonly offered to patients with chronic pain [95, 202]. CBT and ACT may have some benefits for the reduction of pain, but they have primarily been found to be effective for the reduction of patients' psychological distress and functional disability (for reviews, see [45, 217]). Finally, pharmacological interventions are also commonly used for the management of patients with chronic pain. Some of the most common include the use of nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants, muscle relaxants, antidepressants, and anxiolytics/sedatives [31, 43, 58, 107, 116]. Opioids are also commonly prescribed for patients who report moderate to severe pain [21], as will be discussed in the sections below.

1.5. The use of opioids for the management of chronic pain

In the last two decades, there has been a rise in the prescription opioids for patients with chronic noncancer pain. In part due to the high prevalence of chronic pain problems in North America, rates of opioid prescription skyrocketed in the early 2000s. This was also driven by the voices from the pharmaceutical industry and others who believed chronic pain conditions to be poorly managed. Those voices raised concerns about chronic pain being undertreated, which led to more liberal opioid prescribing by clinicians involved in the management of patients with chronic pain. Following this, opioid prescription rates rose staggeringly. By 2010, as many as one in four Canadians received at least one opioid prescription per year [57], making Canada the second highest consumer of opioids worldwide behind the United States [21, 57, 132]. This drastic increase in the rate of opioid consumption had controversial consequences, including increases in opioid-

related intoxications and opioid overdose deaths. Data from the Public Health Agency of Canada [140] indicate that the vast majority of opioid-related deaths occur among users of non-pharmaceutical opioids (e.g., illicitly manufactured fentanyl), suggesting that most of these deaths did not involve medical users of opioids (e.g., patients with chronic pain being prescribed opioids). However, opioid-related deaths also occurred among users of pharmaceutical opioids, which could have included a subset of patients using opioids for chronic pain.

Although most opioid-related intoxications, emergency room visits, and opioid overdose deaths involve illicit opioid users, many concerns remain about the potential problems that may accompany long-term opioid therapy among patients with chronic pain. Long-term opioid therapy has been defined as daily or near-daily use of opioids for at least 90 consecutive days [34]. It is first important to highlight that opioids will likely continue to have a role in the management of some patients with chronic noncancer pain. A recent systematic review and meta-analysis by Busse et al. [21] involving more than 95 randomized controlled trials (RCTs) testing the efficacy/effectiveness of opioids in chronic pain populations indicated that opioids are superior to placebo and non-opioid alternatives for improving pain and function. However, opioid treatment effects were small and the bulk of studies supporting the benefits of opioids were based on RCTs lasting less than six months. Treatment benefits remain but only marginally so [21]. The association between opioids and pain relief was reduced when looking at longer periods of time, most likely due to the effects of opioid tolerance and opioid-induced hyperalgesia [21]. Thus, the effectiveness of opioids is reduced over time and requires higher doses, which is not optimal from a pain management standpoint. Questions have thus been raised concerning the longer-term effectiveness of opioids for the management of chronic pain [21, 33], but for some patients opioids may represent the only effective treatment available.

1.6. Opioid misuse and addiction

Despite the potential analgesic benefits of opioids, several studies have shown that long-term opioid therapy may be accompanied by problems such as opioid misuse and addiction among patients with chronic pain. Opioid misuse refers to the use of opioids differently from how they were prescribed [201, 209]. Opioid misuse behaviours can include taking more opioids than prescribed, taking opioids for other reasons than pain (e.g., to improve mood or sleep), using unsanctioned substances in addition to opioids, or borrowing opioids from others. Evidence from around 40 studies indicates that roughly 20-30% of patients with chronic pain exhibit opioid misuse behaviours [209]. Although certain types of opioid misuse behaviours are viewed as more severe than others [115, 135, 166, 172], the repeated misuse of opioids may ultimately cause health problems and may contribute to opioid addiction [42, 63, 172].

From a diagnostic standpoint, opioid addiction refers to patients meeting criteria for a diagnosis of opioid use disorder (OUD) based on a specific set of diagnostic criteria that were put forward by the American Psychiatric Association in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) [2]. In the DSM-5, opioid use disorder is defined as a problematic pattern of opioid use leading to clinically significant impairment or distress. It is manifested by a certain number of signs and/or symptoms that are assessed in the context of diagnostic interviews with patients. Among patients with chronic pain, evidence indicates that up to 10% of patients present with an opioid use disorder [209]. Patients with chronic pain with a comorbid opioid use disorder are challenging to treat [32, 150, 151] and usually require specialized and/or integrated care simultaneously targeting patients' pain and opioid addiction problems [9, 110, 112]

1.7. Factors associated with opioid use problems in patients with chronic pain

In patients with chronic pain, opioid use problems such as opioid misuse and addiction have been linked to specific factors, including opioid treatment characteristics. More specifically, higher rates of opioid misuse and OUD have been observed among those using certain types of opioids (i.e., Schedule I-II opioids [30, 176]) as well as higher doses of opioids [47, 48, 82, 176]. However, many patients taking high doses of opioids do not show signs of opioid misuse and do not meet criteria for opioid use disorder, suggesting that these problems cannot be solely explained by the basic pharmacological properties of opioids. Considerable evidence has now accumulated indicating that a certain patient characteristics may also increase susceptibility to opioid use problems among patients with chronic pain.

One common assumption in the area of pain and opioids is that patients misuse (e.g., overuse) opioids because of their pain. Interestingly, in previous studies conducted in patients with chronic pain, the magnitude of correlations between patients' self-reports of clinical pain intensity (e.g., 0-100 on a numeric rating scale) and opioid use problems have been found to be modest, at best [148, 149, 223]. In several other studies, the associations between patients' reports of pain intensity and opioid use problems were not even significant [24, 75, 114, 115, 154]. Taken together, results from these studies suggest that patients do not develop opioid use problems simply because they experience high levels of pain.

A number of sociodemographic factors have been associated with elevated rates of opioid misuse and OUD in patients with chronic pain. For instance, higher rates have been observed among men [59, 149, 203] and younger patients [47, 75, 149, 203]. In this population, though, clinical and psychological variables appear to be stronger predictors of opioid misuse and OUD. In previous studies, elevated rates of opioid misuse and OUD have been consistently observed among patients presenting with a lifetime history of mental disorder(s) [12, 13, 36, 98] or with a lifetime history of any

substance use disorder(s) [12, 13, 82, 203]. Other psychological factors that have been strongly linked to heightened rates of opioid use problems in patients with chronic pain using opioids include symptoms of negative affect such as anxiety [114, 154, 13, 130, 146, 147, 149], depression [59, 75, 134, 191 49, 50, 130], and anger [73, 78]. Higher rates of opioid use problems have also been observed among those with greater levels of catastrophizing [4, 24, 78, 115] and distress intolerance [126].

1.8. Opioid craving

Opioid craving is another variable that has received attention in previous research examining the factors associated with opioid use problems among patients with chronic pain. Opioid craving has been defined as the subjective desire or urge to consume opioids [41, 96, 118, 190]. The concept of craving has long been invoked in the substance use literature to explain the development and persistence of various types of substance use problems (for reviews, see [41, 190]). Opioid craving has also emerged as one of the strongest determinants of opioid misuse among patients with chronic pain who are prescribed long-term opioid therapy [109, 113, 114, 211]. Opioid craving has been included as one of the potential criteria for the diagnosis of opioid use disorder in the DSM-5 given its predominant role across most substance use disorders and its association with relapse following treatment [79, 96, 97, 153]. In a study conducted among > 1500 patients with chronic pain prescribed opioids [208], craving was reported in up to 65 % of patients meeting diagnostic criteria for OUD.

1.9. Perceived injustice: Its importance in the context of chronic pain and its potential contribution to opioid use problems

People want to believe that the world is fair: that good things happen to good people and bad things happen to bad people. For many patients suffering from chronic pain, though, life is experienced with a recurrent sense of injustice. In addition to experiencing persistent physical and

emotional suffering, the experience of multiple losses (e.g., loss of function, independence, or financial security) may give rise to perceptions of injustice [26, 28, 157, 180, 181, 194] . Some chronic pain patients suffer on a daily basis with no explainable cause or any end in sight, and some patients may find themselves isolated from their peers as well as dismissed by the healthcare system all by no fault of their own. The experience of pain and associated losses resulting from someone else's actions or negligence (e.g., pain following motor vehicle accident or unsafe working conditions) is also likely to give rise to perceptions of injustice [26, 28, 157, 180, 181, 194]. Clinical experience tells us that themes of injustice are often reflected in patients' verbalizations such as "*nothing will ever be the same*", "*nothing will ever make up for what I have gone through*", "*I can't believe this happened to me*", and "*it all seems so unfair*". These types of verbalizations reflect the perceived unfairness of suffering, and the magnitude of loss consequent to pain.

The frequent occurrence of injustice-related themes as part of chronic pain patients' clinical presentations has sparked interest in examining the impact of perceived injustice on pain-related outcomes. In the chronic pain literature, perceived injustice has been defined as a cognitive appraisal involving elements of blame, unfairness, and the severity or irreparability of pain-related loss [158, 179]. Perceived injustice has been linked to several negative pain-related outcomes, such as heightened pain intensity, pain-related disability, and decreased quality of life (for a review, see [26]). Perceived injustice is also been associated with psychological problems such as negative affect (e.g., depression, anxiety and anger) [26, 29, 156, 158, 170, 183, 184, 221, 222] and pain catastrophizing [111, 171, 179, 184]. Importantly, perceived injustice has been found to be a significant obstacle to improvement among patients with pain undergoing treatment [159]. Associations between perceived injustice and negative pain-related outcomes have been observed among patients suffering from various types of chronic pain conditions (for reviews, see [25, 181]).

While the negative impact of perceived injustice on pain-related outcomes has been well-documented [26, 181], little is known on the association between injustice and opioid-related outcomes. In two different studies, patients with chronic pain who reported high levels of injustice were more likely to be prescribed long-term opioid therapy [27 29]. The reasons why patients with high levels of injustice are more likely to be prescribed opioids remains unclear. In one of these studies [27], patients' pain behaviours (i.e., pain expressiveness) mediated the association between perceived injustice and opioid prescription. It was suggested that patients with high levels of perceived injustice might display more pain behaviours as a means of communicating the intensity of their suffering and/or losses [27, 181, 185], which might promote opioid prescribing. While this will need to be clarified in future research, the higher rates of opioid prescribing among patients with high levels of injustice falls in line with those of other studies indicating that patients who present with psychological problems (e.g., depression) are more likely to be prescribed long-term opioid therapy than patients without a history of mental health problems [14, 46, 175], even if this is not supported by opioid prescribing guidelines [20, 40]. This phenomenon, which was termed "adverse selection" [6, 174, 177], might also apply to patients who report high levels of injustice, and this could contribute to explaining why they are more likely to be prescribed opioids.

Although research has shown that patients with high levels of perceived injustice are more likely to be prescribed opioids than those with low levels of injustice, it remains unknown whether perceived injustice is associated with opioid use problems over the course of long-term opioid therapy. As noted earlier, the bulk of research that has been conducted to examine the psychological factors associated with opioid use problems have focused on negative affect (i.e., depression, anxiety) or catastrophizing. Given that perceived injustice is known to be associated with heightened negative affect [26, 29, 156, 158, 170, 183, 184, 221, 222] and pain catastrophizing [111, 171, 179, 184],

there is reason to believe that injustice might also contribute to opioid use problems. To date, however, this has yet to be investigated.

Questions also remain concerning the association between perceived injustice and opioid craving. In patients with chronic pain, higher levels of pain intensity have been found to be associated with greater levels of opioid craving, but research indicates that pain intensity is not the sole reason why patients crave opioids [108, 117]. Psychological variables such as pain catastrophizing and negative affect, for instance, have been shown to be associated with opioid craving over and above patients' pain intensity levels [64, 83, 114]. Negative affect and catastrophizing, though, cannot fully explain the variability in opioid craving observed across patients with chronic pain, and it is possible that perceived injustice also contributes to patients' desires and/or urges to use opioids (i.e., opioid craving). An association between perceived injustice and opioid craving could be possible due to a number of reasons. For instance, perceptions of injustice may contribute to enhancing patients' daily levels of pain intensity [25, 158, 185, 193], which in turn could lead to heightened opioid craving. Similarly, perceived injustice might contribute to enhancing patients' daily levels of negative affect and catastrophic thinking [111, 179, 181], which in turn might contribute to heightened levels of opioid craving. To date, the factors that might potentially underlie the association between perceived injustice and opioid craving among patients with chronic pain have yet to be explored. Advancing knowledge in this area would not only extend previous work conducted on injustice and opioids, but would also bring new insights into why some patients with chronic pain exhibit opioid use problems. From a clinical standpoint, this might pave the way to the development of new psychological interventions for preventing or minimizing opioid use problems among patients with chronic pain who are prescribed opioids.

1.10. Thesis objectives

The first objective of the present thesis was to examine the association between perceived injustice and prescription opioid misuse in patients with chronic pain. The second objective was to examine the association between perceived injustice and opioid craving. Finally, the potential mediating role of pain intensity, negative affect, and pain catastrophizing on the association between perceived injustice and opioid craving was examined.

2.0. Methods

2.1. Study design and participants

This was a longitudinal, observational, cohort study conducted among patients with chronic non-cancer pain (CNCP) prescribed long-term opioid therapy. Patients (n = 103) were recruited from primary care settings as well as from the McGill University Health Centre (MUHC) Alan Edwards Pain Management Unit (AEPMU), a tertiary care pain clinic setting. Participants from the present study were part of a larger study designed to examine the determinants of opioid misuse [62], but this is our first report examining the association between perceived injustice and opioid use problems. All participants underwent a telephone screening in order to ensure they met eligibility criteria. Patients included in the study met the following inclusion criteria: 1) aged 18 or older, 2) chronic (≥ 6 months) non-cancer pain, 3) currently prescribed long-term (≥ 3 months) opioid therapy, 4) taken orally, 5) and on a daily basis.

Patients were excluded from participation if they met any of the following criteria: 1) use of rectal, intrathecal, intravenous, intramuscular, or subcutaneous routes of opioid administration, 2) use of opioid antagonists, mixed agonist/antagonist opioid formulations, 3) cognitive impairment (e.g., intellectual disability or dementia) preventing completion of study procedures.

2.2. Procedures and measures

All study procedures were approved by the Research Ethics Board of the Research Institute of the McGill University Health Centre (RI-MUHC). Eligible patients were scheduled for a baseline assessment laboratory visit at the Montreal General Hospital (see section 2.2.1) and were then followed longitudinally for 14 consecutive days using daily diary procedures (see section 2.2.2).

2.2.1. Baseline visit

Upon arrival at the hospital, all patients were invited to read and sign a consent form. They were accompanied by a trained research assistant who answered any questions about the study. Patients were then asked to complete a demographic questionnaire that assessed sociodemographic characteristics, including patients' age, gender, ethnicity, employment status, education, and marital status. All the medications taken by patients were also reported. Opioid types and doses were recorded through the research assistants' inspection of patients' prescription documentation (i.e., pharmacy printout) or medication containers. Patients were then asked to complete the following questionnaires:

2.2.1.1. The Brief Pain Inventory (BPI; [188]), which was used to assess the number and location(s) of pain. On the BPI body diagram, patients were asked to shade in the areas (i.e., sites) where they experience pain.

2.2.1.2. *The Injustice Experience Questionnaire (IEQ; [179]),* which was used to assess patients' perceptions of injustice. The IEQ contains 12 items that are rated on a 5-point scale ranging from 0 (not at all) to 4 (all the time). The IEQ contains two subscales ("severity/irreparability of loss" and "blame/unfairness") but can also be interpreted using a total

score. The IEQ has been shown to have good internal consistency [179], and the coefficient alpha for the total IEQ in this study was excellent (Cronbach $\alpha = 0.88$).

2.2.1.3. The Drug Abuse Screening Test (DAST; [163]), which was used to assess patients' past-year substance use problems. The DAST is a well-accepted 10-item screening tool that has been used in chronic pain populations to screen for past-year substance use problems involving illicit drugs [136, 152, 165].

2.2.1.4. The Prescription Drug Use Questionnaire (PDUQ; [35]), which was used to assess lifetime personal and family history of substance use problems. The PDUQ has been used in numerous studies conducted among patients with chronic pain prescribed opioids.[8, 35].

2.2.2. Daily diaries

At the end of the baseline visit, patients were given instructions for the completion of daily diaries at home. All daily diaries were completed using REDCap, an electronic data collection software. Once a day for 14 consecutive days, participants were prompted by REDCap to answer questions about pain intensity, negative affect, catastrophizing, and opioid craving (see below for a description of diary items). Patients were prompted to answer diary questions in the evening based on their experiences over the previous 24 hours. All diary entries were date- and time-stamped to ensure validity, to record specific times when diary reports were made, and to monitor patients' compliance.

2.2.2.1. Daily ratings of pain intensity

Patients rated the average level of pain they experienced over the past 24 hours using a visual analogue scale (VAS) that ranged between 0 (no pain) to 100 (extreme pain). This measure is a diary adaptation of the standard VAS item used in the Brief Pain Inventory (BPI; [188]) to assess

pain intensity. The BPI is one of the most commonly used measure to assess pain intensity among patients with chronic pain [188, 88, 44, 116].

2.2.2.2. Daily ratings of negative affect

Patients rated how much they have felt various negative emotions (e.g., afraid, upset, nervous, scared, distressed) in the past 24 hours on a scale that ranged from 0 (not at all) to 4 (extremely). This measure is a diary adaptation of the Positive and Negative Affect Scale (PANAS; [214]), which has been used in numerous studies among patients with chronic pain [38, 55, 56]. Consistent with previous research, negative items were averaged to create a measure of NA [38, 56, 104]. In the present study, the internal reliability coefficients of items assessing NA (Cronbach α = .89) was excellent.

2.2.2.3. Daily ratings of catastrophizing

Daily catastrophizing was assessed using a diary version of the Pain Catastrophizing Scale [37, 173]. Patients reported different thoughts and emotions associated with pain based on the past 24 hours using a scale ranging from 0 (not at all) to 4 (all of the time). The reliability and validity of the daily PCS as a measure of daily catastrophizing has been supported [37], and the internal reliability coefficient of items used to assess catastrophic thinking in the present study (Cronbach α = .89) was excellent.

2.2.2.4. Daily ratings of opioid craving

Patients were asked to rate the level of opioid craving they experienced over the past 24 hours using 3 different items: (1) *How often have you found yourself thinking about your opioid medication and your next opioid doses*? (2) *How often have you experienced a desire to use your opioid medication?* (3) *How often have you craved your opioid medication?* Items were rated on

a VAS that ranged from 0 (never) to 100 (very often). These items were adapted from the Opioid Craving Scale (OCS; [125]) and used in many studies among patients with chronic pain prescribed long-term opioid therapy [114, 117, 213]. These items have been found to have adequate psychometric properties and the internal reliability of craving items in the present study was excellent (Cronbach $\alpha = .94$).

2.2.2.5. Opioid misuse

Opioid misuse was assessed using items from the Current Opioid Misuse Measure (COMM; [23]). COMM items were used to assess the frequency of three distinct types of opioid misuse behaviours (i.e., using more opioids than prescribed, using opioids for symptoms other than pain, borrowing opioids) using the following COMM items: *"In the past 14 days, how often have you had to take more opioid medication than prescribed? How often have you used your pain medicine for symptoms other than pain? How often have you borrowed medication from someone else?"* COMM items were completed at the end of the diary assessment period (i.e., Day 14) using a scale that ranged from 0 (never) to 4 (very often). The internal reliability of COMM items included in the present study ($\alpha = .67$) was acceptable. Several studies have supported the reliability and validity of the COMM for the identification of patients who are misusing opioids over the course of long-term opioid therapy [8, 22, 23, 210].

2.3. Data reduction

All statistical analyses were conducted using IBM-SPSS (version 24). Descriptive statistics for categorical and continuous variables were presented as percentages and means ± standard deviations (SDs), respectively. Unless otherwise specified, all statistical assumptions were met.

Before conducting primary study analyses, a series of analyses were first conducted to examine the potential confounding influence of patient demographics (i.e. age, sex, ethnicity, education, marital status, employment status), opioid regimen characteristics (i.e. opioid types, doses), pain characteristics (i.e., number of pain locations, pain duration), and psychological/psychiatric variables (i.e., past-year substance use problems) on main study outcomes (i.e., opioid craving, opioid misuse). As recommended [167, 216], variables significantly associated with main study outcomes were included as covariates or effect modifiers in main study analyses.

To examine the association between perceived injustice and POM, a series of Spearman correlations were first conducted. These analyses examined the association between total injustice scores (IEQ-Total) and each of the opioid misuse behaviours (i.e., overusing prescription opioids, using opioids for reasons other than pain, borrowing opioids). Analyses were also conducted to examine the associations between IEQ subscales (i.e., severity/irreparability, blame/unfairness) and each of the opioid misuse behaviours.

A multilevel regression analysis was then used to examine the association between perceived injustice and daily opioid craving. Multilevel modeling (MLM) was used given the hierarchical data structure of this study in which repeated opioid craving assessments (Level 1 units) were nested within participants (Level 2 units). In this analysis, opioid craving was used as the outcome variable and perceived injustice (IEQ-total) was used as the independent variable. Separate multilevel regression analyses were also conducted between IEQ subscales (severity/irreparability, blame/unfairness) and opioid craving.

In order to examine the potential mediators of the association between perceived injustice and opioid craving, a multilevel mediation analysis was conducted using the MLmed macro [80].

The mediation analysis examined whether the association between perceived injustice (IEQ-total) and opioid craving was mediated by patients' daily levels of pain intensity, negative affect, and/or catastrophizing. Using MLmed, the mediation analysis allowed to test the mediation (i.e., indirect) effects of each mediator independently (i.e., specific mediation/indirect effects) while controlling for all other mediators included in the model [139, 161]. In the present multilevel mediation analysis, 95% Monte Carlo confidence intervals (MCCIs) with 10,000 re-samples were computed and used to test the significance of all indirect effects. As recommended, estimates of indirect effects were considered significant when zero was not included within the confidence intervals [80, 139].

All multilevel models described above were carried out using maximum-likelihood (ML) estimation and included a first-order autoregressive variance covariance matrix (AR1) to account for the autocorrelation between repeated measures. As recommended, all independent variables were centered before being entered in multilevel models [54, 133], and effect sizes were estimated by calculating the percentage reduction in unexplained variance at the within-person level relative to the unexplained variance of the null model. Multilevel analyses did not require any data imputation given that MLM can account for missing Level 1 data [138, 162]. Compliance with the diary protocol was very high, with an averaged completion rate of 96.4% across all assessment time points and daily diary variables (i.e., pain intensity, negative affect, catastrophizing, opioid craving). Analyses indicated that patients with and without missing data did not differ significantly on any of the main study variables (all p's > .05).

3.0. Results

3.1. Descriptive statistics

Descriptive statistics for study measures are presented in Table 1, along with the types of opioid medications used by participants. The sample had a fairly even distribution of both sexes

(50.5% male) and mostly included Caucasians (80.6%). On average, the pain duration of participants was 12.4 years (SD = 11.9). The average morphine equivalent daily dose (MEDD) for this sample was 67.67 mg/d (SD = 101.12), with most participants taking short-acting opioids (86.4%), some taking long-acting opioids (39.8%), and others taking both types of opioids (26.2%).

Before conducting main study analyses, the potential confounding influence of patient demographics, opioid regimen characteristics, pain characteristics, and psychological/psychiatric variables on primary study outcomes was examined. Results indicated that sex, ethnicity and past-year substance abuse (DAST-10) were significantly associated with opioid craving. More specifically, men reported significantly greater opioid craving than women (B = 9.15, p = .041), non-Caucasians reported significantly greater opioid craving than Caucasians (B = 13.12, p = .020), and DAST-10 scores were significantly associated with opioid craving (B = 4.11, p = .001). Past-year substance abuse problems (i.e., DAST-10) was the only variable significantly associated with opioid misuse, with greater DAST-10 scores associated with more frequent opioid misuse behaviours (*rs* = .20, p = .045). None of the other variables were significantly associated with main study outcomes (i.e., opioid craving, opioid misuse).

3.2. Association of perceived injustice and opioid misuse

The relationship between perceived injustice and opioid misuse was examined using Spearman correlations. Results indicated that IEQ-total scores were not significantly associated with any of the opioid misuse behaviours (all p's > .05). IEQ subscales (i.e., IEQ-severity/irreparability, IEQ-blame/unfairness) were also not significantly associated with any of the opioid misuse behaviours (all p's > .05). The frequency of different types of opioid misuse behaviours is shown in Figure 1.

3.3. Association of perceived injustice and opioid craving

A multilevel linear analysis was conducted to assess the association between perceived injustice and daily levels of opioid craving. Results indicated that greater levels of injustice were associated with higher daily levels of opioid craving (B = .45, p = .032). Multilevel linear analyses were then conducted using IEQ subscales (i.e., IEQ-severity/irreparability, IEQ-blame/unfairness). Analyses indicated that the blame/unfairness subscale was not significantly associated with opioid craving (B = .60, p = .077). However, a significant association was found between the severity/irreparability subscale and opioid craving (B = .98, p = .026). The associations between perceived injustice and opioid craving are shown in Figures 2a-c.

3.4. Mediators of the association between perceived injustice and opioid craving

The mediating roles of pain intensity, negative affect, and pain catastrophizing in the association between perceived injustice and opioid craving was assessed using the MLmed macro [80]. As can be seen from Figure 3, all a-paths were significant, as perceived injustice was associated with all potential mediators. More specifically, greater levels of perceived injustice were associated with higher daily levels of pain intensity (B = .35, p = .025), negative affect (B = .13, p < .001), and catastrophizing (B = .10, p < .001). The multilevel mediation analysis then examined the associations between mediator variables and opioid craving (b-paths). Results indicated that pain intensity (B = .37, p = .003) and catastrophizing (B = 3.47, p = .003) were both significantly associated with opioid craving. However, negative affect was not (B = 1.14, p = .074). The association between perceived injustice and opioid craving (path c') was not significant (B = - .24, p = .186), suggesting that this association was mediated by one or more of the mediator variables included in the analysis. Results revealed that the indirect (i.e., mediation) effect of catastrophizing was significant (p < .05), indicating that this variable mediated the association between perceived

injustice and opioid craving. The mediation effects of NA and pain intensity were not significant ($p > .05$).

4.0. Discussion

The first objective of the present study was to examine the association between perceived injustice and prescription opioid misuse in patients with chronic pain on long-term opioid therapy. The second objective was to examine the association between perceived injustice and opioid craving. Lastly, this study sought to examine whether the association between perceived injustice and opioid craving would be mediated (i.e., explained) by patients' daily levels of pain intensity, negative affect, or catastrophizing.

Perceived injustice and opioid misuse

In the present study, we assessed three distinct types of opioid misuse behaviours that are commonly observed among patients with chronic pain who are prescribed long-term opioid therapy. This includes using more opioids than prescribed (i.e., opioid overuse), using opioids for other symptoms than pain, and borrowing opioids from others. Results from correlation analyses indicated that patients' levels of perceived injustice were not significantly associated with any of these opioid misuse behaviours. The non-significant associations between perceived injustice and opioid misuse behaviours were unexpected given that perceived injustice is linked to other psychological variables known to be associated with opioid misuse, such as catastrophizing [4, 85, 131] and negative affect [66, 114]. Rates of opioid misuse behaviours in our study were consistent with those observed in other studies (for a review, see [209]), suggesting that the non-significant association between perceived injustice and opioid misuse is unlikely to be due to patient underreporting of opioid misuse. On the basis of our results, it thus seems like psychological factors such as negative affect and catastrophizing are likely to be stronger determinants of opioid

misuse than perceptions of injustice among patients with chronic pain who are prescribed long-term opioid therapy.

Perceived injustice and opioid craving

One of the novel findings from the study was the significant association between perceived injustice and opioid craving. In particular, greater scores on the severity/irreparability subscale of the IEQ were associated with higher daily levels of opioid craving. Given that the severity/irreparability subscale of the IEQ refers to patients' perceptions of the severity and/or irreparability of their pain-related loss, one possible explanation for this finding would be that patients who perceive their pain conditions as irreversible experience more severe pain than those who do not. Greater pain intensity has previously been linked to greater levels of perceived injustice [156,195] as well as opioid craving [117]. As such, perceptions of severity/irreparability might lead to higher levels of opioid craving due to the high levels of pain intensity experienced by patients. In our multilevel mediation analysis, pain intensity did not mediate the relationship between perceived injustice and opioid craving, but this possibility still needs to be considered.

There are other factors that could possibly explain why patients' perceptions about the severity/irreparability of their pain was associated with greater opioid craving. In past research, perceptions of severity/irreparability of pain have been linked to negative affect [158, 221] and feelings of helplessness [111]. Several studies have shown that negative affect is linked to higher levels of opioid craving among patients with chronic pain [64, 83, 114, 117], suggesting that negative affect might explain, at least in part, the association between patients' perceptions of injustice and opioid craving. In our study, negative affect did not emerge as a significant mediator of the association between injustice and opioid craving. However, patients with higher levels of perceived injustice reported greater levels of negative affect, and patients' daily levels of negative affect were

associated with heightened opioid craving in univariate analyses. This suggests that negative affect is likely to remain an important psychological variable underlying the association between perceived injustice and opioid craving. Among patients with high levels of negative affect, self-medication is often invoked to explain the drive to use substances, including opioids, [69, 70, 99], so the alleviation of negative affect should be considered in future research when examining associations between perceived injustice and opioid craving among patients with chronic pain. In future research, other dimensions of negative affect that were not assessed through our daily diary assessments, such as feelings of anger or hostility, should also be considered. In patients with chronic pain, perceived injustice is viewed as cognitive antecedent to anger [158, 181, 197] , which could contribute to heightened opioid craving similarly as other negative affective states. Interestingly, laboratory studies have shown that anger is associated with dysfunctions in endogenous opioid systems [16, 17, 19] which could contribute to explaining interrelations between perceived injustice, anger, and opioid use problems in patients with chronic pain.

Results from our mediation analysis suggest that catastrophizing is likely to explain, in part, the association that was observed between perceived injustice and opioid craving. In previous studies conducted among patients with chronic pain, catastrophizing has been linked to both opioid craving [118, 212] and perceived injustice [111, 179, 181], including the severity/irreparability subscale of the IEQ [111]. In the present study, results indicated that daily pain catastrophizing mediated the association between injustice and opioid craving, suggesting that patients' perceptions of injustice might contribute to greater daily catastrophic thoughts, which in turn might contribute to opioid craving. This finding was significant even when controlling for other important covariates, such as patients' daily levels of pain intensity and negative affect. This is important, as it suggests that

patients with high levels of injustice and daily levels of catastrophizing do not crave opioids solely because they experience higher levels of pain, anxiety, or depressive symptoms.

Given the overlap and close associations between perceptions of injustice and catastrophic thoughts, there is reason to believe that these two psychological variables lead to opioid use problems in a similar manner. For instance, research indicates that patients with high levels of injustice and catastrophizing tend to rely on passive coping strategies for the management of pain [28, 52, 181, 182], which may not only interfere with patients' adjustment to chronic pain, but also promote reliance on medications such as opioids [90, 92, 198]. Previous studies have shown that patients who are less inclined to rely on active coping strategies when experiencing pain are more likely to crave opioids and, in turn, to engage in opioid misuse behaviour [65 68]. Deficits in pain coping skills might thus contribute to explaining opioid use problems in patients with chronic pain who present with high levels of injustice and catastrophic thinking.

Patients' deficits in pain coping skills might stem, in part, from an external attribution style, a maladaptive cognitive pattern leading patients to attribute their pain and pain-related losses to external reasons [157, 197]. The attribution of negative events to external causes has been shown to be associated with anger and blame [215], which are core components of perceived injustice . In patients with chronic pain, external attributions in relation to pain and pain-related loss have also been linked to helplessness [18, 90], a core feature of catastrophizing [52, 182]. Given that external attributions promote the adoption of passive coping strategies [90], patients' attributional styles might also contribute to an increased reliance on opioids and to heightened opioid craving. Future research will be needed to further explore the degree to which patients' attribution styles and pain coping strategies play a role in opioid craving and opioid use problems among patients with chronic pain who present with high levels of injustice and catastrophizing.

There are other psychological factors that are common to patients with high perceived injustice and catastrophizing that could have led to heightened daily levels of opioid craving in our study. For instance, attention biases to sensory and affective pain information have been observed both among patients with perceived injustice [196] and catastrophizing [204, 205] in the context of laboratory studies, as these patients pay more attention to pain-related cues and have difficulty disengaging their attention from pain. These laboratory findings are directly in line with the clinical presentations of patients with high levels of perceived injustice and catastrophizing, who are characterized by a tendency to ruminate about pain, suffering, and pain-related losses. Although speculative, it is possible that this attention bias extends to opioid-related cues. Opioid-related cues are known to play an important role in triggering opioid craving, both among illicit [61, 224] and medical users of opioids [66]. Opioid-related cues can be external (e.g., places or people) or internal (e.g., mood states) [81, 129]. Similarly to illicit opioid users, medical users of opioids, such as patients with chronic pain, have been found to experience significantly more attentional bias toward opioid cues [67]. Furthermore, opioid attention bias was significantly associated with opioid craving in this population [67]. Given that patients presenting with high levels of perceived injustice and catastrophizing are characterized by attention biases toward pain information [142, 189, 195], it is possible that these patients also show opioid-related attention biases, which could contribute to heightened levels of craving and opioid use problems. Future research will be needed to determine the degree to which attentional biases play a role in opioid use problems among patients with high levels of perceived injustice and catastrophizing.

Theoretical implications

Findings from the present thesis could have implications for the refinement of theoretical models that have recently been proposed to account for opioid use problems among patients with

chronic pain. It is first worth specifying that numerous theoretical models of craving and substance use disorders have been proposed over the past few decades in the broader substance use literature (for reviews, see [41, 60, 164]). However, none of these models have included pain as a central feature. In recent years, pain has been given a greater consideration in conceptual models of substance use problems, particularly given the well-documented problems associated with the use of opioids.

Conditioning (i.e., learning) models of addiction have mainly focused on the role of reward in the development of addiction [1, 10, 81, 143-145, 207, 218-220]. They are largely divided into two camps: negative reinforcement theories of addiction and positive reinforcement theories of addiction [143]. Negative reinforcement theories posit that drug-seeking behaviours are driven by the desire to avoid the unpleasant experiences associated with withdrawal [101, 143] or allostasis [72, 100, 102]. Contrary to the negative reinforcement theory, the positive reinforcement theory suggests that drug-taking occurs not out of a need to avoid an unpleasant state, but rather to induce a pleasant one [143, 218, 220]. In other words, people take drugs to experience the positive hedonic feelings they induce. It is now generally acknowledged that both reinforcement processes play a role in the maintenance of substance use problems [101, 143, 220]. In the context of our study, the finding that day-to-day elevations in negative affect and catastrophizing (two unpleasant emotional/psychological states) were associated with heightened levels of opioid craving might suggest that negative reinforcement processes contributed, in part, to patients' opioid craving states.

Building upon existing theoretical models of addiction, Ballantyne and colleagues [7] recently put forward a theoretical framework to account for opioid use problems among patients with chronic pain. More specifically, it is proposed that opioid use problems in patients with chronic pain involve three stages: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation [7, 103]. In this model, it is assumed that long-term opioid use leads to

neuroadaptations at various levels of the central nervous systems, and that separate neural circuits are responsible for each of these stages [7, 103]. The binge/intoxication stage is thought to be characterized by reward and incentive salience associated with opioid use [7, 103], and this stage has been linked to neuroadaptations in the basal ganglia. The withdrawal/negative affect stage is thought to involve repeated negative emotional states and stress, and this stage has been linked to alterations in the extended amygdala and the habenula [7, 103]. In their model, Ballantyne et al. [7] argued that chronic pain patients might not show any evidence of binge/intoxication, as chronic pain patients use opioids primarily for pain relief rather than for their hedonic (i.e., pleasurable) effects. It is now well-acknowledged that physical dependence to opioids arises in virtually all patients who are maintained on long-term opioid therapy [6, 91], and some of the transient opioid withdrawal symptoms experienced by daily opioid users are likely to play a stronger role in the experience of opioid craving and development of opioid use problems in these patients. Ballantyne and colleagues also argued that patients' negative affect, in part caused by withdrawal symptoms and the underlying dysregulations in neural mechanisms involved in mood/affect regulation, contributes to patients' recurrent preoccupation and desires (i.e., cravings) towards the use of opioids. In our study, we found a fairly strong association between patients' levels of perceived injustice and daily levels of negative affect. Proceeding from the model put forward by Ballantyne et al [7], patients' psychological characteristics, such as perceived injustice, might thus contribute indirectly to opioid use problems in part due to their impact on negative affect.

Clinical implications

Findings from the present study could have implications for clinicians involved in the management of patients with chronic pain who are prescribed long-term opioid therapy. Although preliminary, our findings suggest that targeting perceived injustice could be helpful for reducing

opioid use problems in patients with chronic pain. Our findings suggest that reducing patients' levels of perceived injustice may lead to reductions in opioid craving. Given that opioid craving is one of the strongest determinants of prescription opioid misuse [64, 108, 114, 118, 211], the use of interventions to minimize patients' perceptions of injustice and opioid craving might, in turn, contribute to minimizing opioid use problems. As noted by Carriere et al. [26], there is a considerable knowledge gap regarding the pathways through which perceived injustice leads to negative pain-related outcomes. As such, there are currently no intervention programs that specifically target perceived injustice [183]. In previous work, it was found that undergoing physical rehabilitation did not contribute to a reduction in patients' levels of injustice, even if this intervention led to reductions in pain [179]. This suggests that interventions solely focused on pain reductions may not be sufficient to attenuate patients' levels of injustice. Recent research has found psychological interventions aimed at reducing perceived injustice using dialectical behaviour therapy (DBT) could be useful [184]. Furthermore, a recent review by Bissel et al. [11] suggested that although cognitive-behavioural therapy (CBT) may be effective in reducing perceptions of injustice in people who do not have high levels of perceived injustice, "third wave" psychotherapies such as acceptance and commitment therapy (ACT) and mindfulness-based stress reduction may lend themselves better to the cognitive attributes of injustice [11]. Furthermore, a study using risk-targeted behavioural activation intervention specifically targeting perceptions of injustice was successful in reducing them [184]. However, this same study found that although early treatment changes in perceived injustice predicted reductions in late treatment changes in depressive symptom severity, the inverse was not true [184]. These findings raise questions regarding the potential effectiveness of psychological interventions targeting depression symptoms as a way to reduce perceptions of injustice. Future research into possible perceived injustice interventions could give clinicians new

treatment options to help alleviate the negative consequences of perceived injustice on chronic pain patients as well as on opioid-related outcomes [11, 26, 183, 184].

Limitations

There are some limitations that must be considered when interpreting finding from the present thesis. First, our study involved primarily Caucasians, which limits the generalizability of our findings. Ethnic disparities in chronic pain and pain management have been well documented [3, 76, 141], and research among patients with chronic pain has identified ethnic differences in perceived injustice [194]. Second, despite the use of a longitudinal diary study design that allowed us to examine patients' day-to-day levels of pain, psychological function, and opioid craving, patients provided diary reports only once a day at a fixed time. Although this is a commonly used daily diary study method [15, 160, 169], this might have introduced a certain degree of predictability and influenced patients' reports. Third, our assessment of opioid misuse was performed at a single time point, retrospectively. Future work should consider incorporating daily assessments of opioid misuse to minimize retrospective bias. Another consideration when interpreting the results of this study is the nature of the mediation model that was tested. Our model was based upon previous research on the factors known to be associated both with perceived injustice and opioid craving (i.e., pain intensity, NA, catastrophizing). However, in our model these variables were treated as potential consequences of injustice, and it is conceivable that these variables also contribute to fuelling patients' daily levels of injustice. Future studies will be needed to firmly establish the directionality of associations between perceived injustice, daily pain intensity, psychological function, and opioid craving.

Future directions

Despite these limitations, the present study provides new insights into our understanding of the factors that might contribute to opioid use problems in patients who experience high levels of perceived injustice. One of the key findings of the present study is that the association between perceived injustice and opioid craving is mediated (i.e., explained) by catastrophizing. In other words, our findings suggest that patients who experience high levels of perceived injustice tend to engage in greater catastrophic thinking, which in turn might contribute to opioid craving. Future research will be needed to examine whether the association between injustice and opioid craving might be mediated by other negative emotional/affective states that were not assessed in the present study, such as anger, which has been linked to perceived injustice in patients with chronic pain [29, 158]. Findings from our study are particularly novel given that the bulk of previous work conducted on injustice has primarily focused on the association between injustice and pain-related outcomes [26]. To our knowledge, this is the first study to show that injustice might contribute to opioid use problems (e.g., opioid craving) in patients with chronic pain. Additional studies will be needed to determine if reductions in patients' injustice perceptions might be accompanied by reductions in daily opioid craving levels and opioid misuse behaviours. Future studies reviewing this topic may further elucidate the feasibility and efficacy of psychological interventions targeting perceptions of injustice. This might ultimately lead to improved pain management outcomes and lower opioid-related harms among patients with chronic pain who are prescribed long-term opioid therapy.

List of Tables and Figures

Table 1
Sample characteristics and descriptive statistics (N= 103)

	Mean (SD) or %
Baseline measures	
Sex (% men)	50.5%
Age (years)	52.8 (12.3)
Martial status (% married/relationship)	44.7%
Education level (≥ high school)	86.4%
Ethnicity (% Caucasian)	80.6%
Tobacco use (% smokers)	31.3%
Frequency of tobacco use (cigs/day)	15.5 (11.2)
Frequency of alcohol use (drinks/week)	3.0 (11.2)
Past-year substance use problems (DAST-10)	2.4 (1.8)
Perceived injustice (1 - 45)	26.5 (10.8)
Pain characteristics	
Pain duration (years)	12.4 (11.9)
Back	72.8%
Legs/feet	67.0%
Neck	41.7%
Shoulders/arms	40.8%
Hips/knees	37.9%
Head/face	18.6%
Chest/abdomen	13.6%
Opioid regimen characteristics	
MEDD (mg/d)	67.7 (101.1)
Short-acting opioid users	86.4%
Long-acting opioid users	39.8%
Long-acting and short-acting opioid users	26.2%
Daily measures	
Average daily pain intensity (0 - 100)	56.4 (17.0)
Average daily negative affect (5 - 25)	9.9 (3.7)
Average daily catastrophizing (3 - 15)	7.1 (2.3)
Average daily opioid craving (0 - 100)	38.6 (23.0)

Note. Values in parentheses are standard deviations. Average daily variables (i.e., pain intensity, negative affect, catastrophizing, opioid craving) represent aggregated scores across the 14-day diary period.

Figure 1
Frequency of opioid misuse behaviours

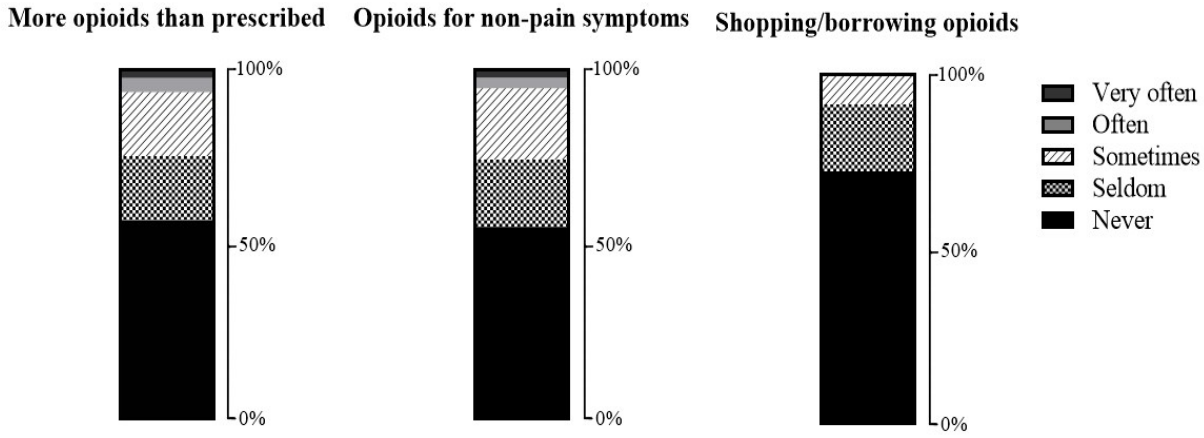


Figure 2a
Association between total score of perceived injustice and opioid craving

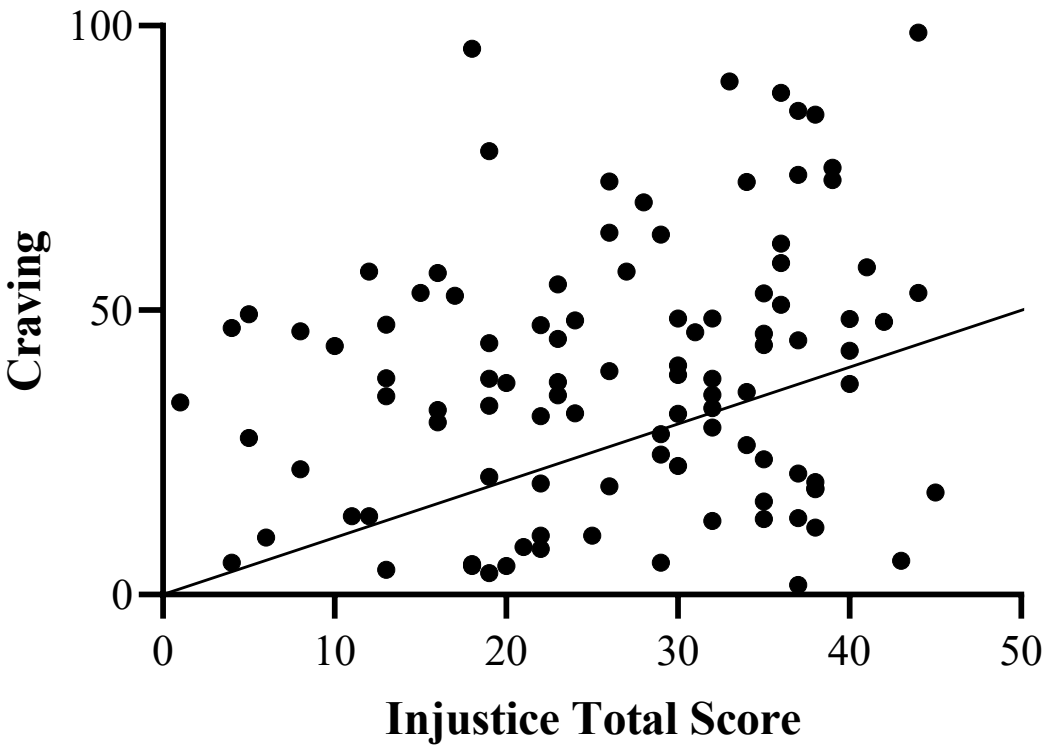


Figure 2b
Association between blame/unfairness score of perceived injustice and opioid craving

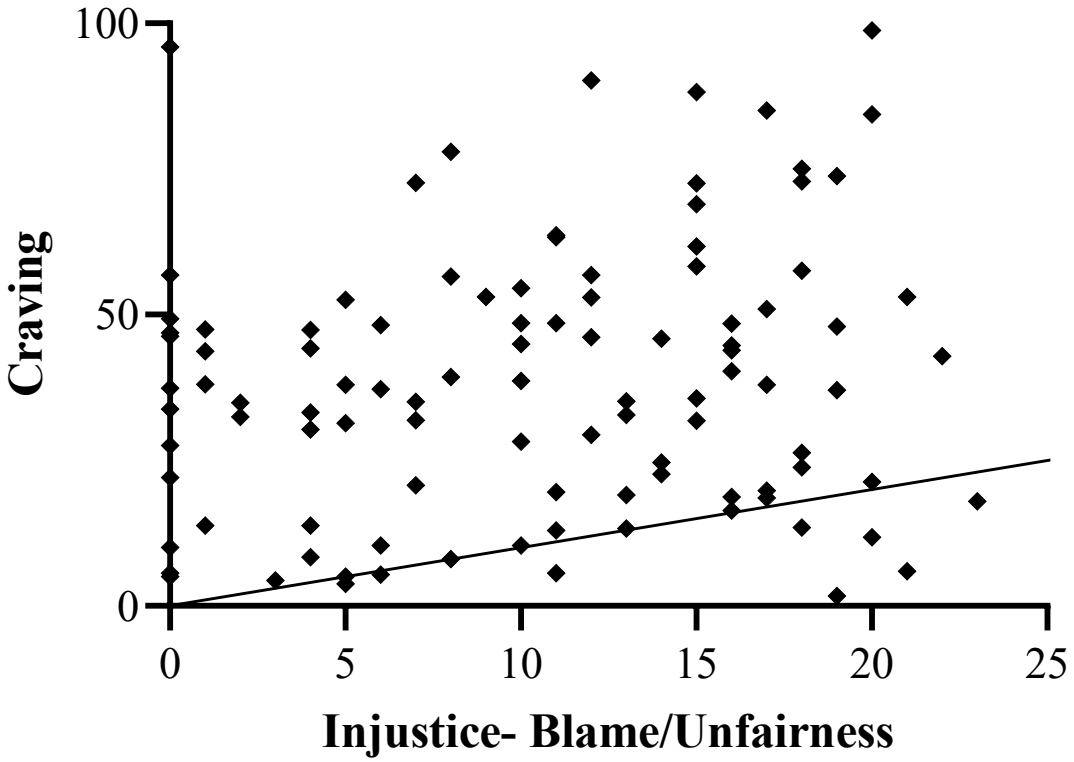


Figure 2c
Association between severity/irreparability score of perceived injustice and opioid craving

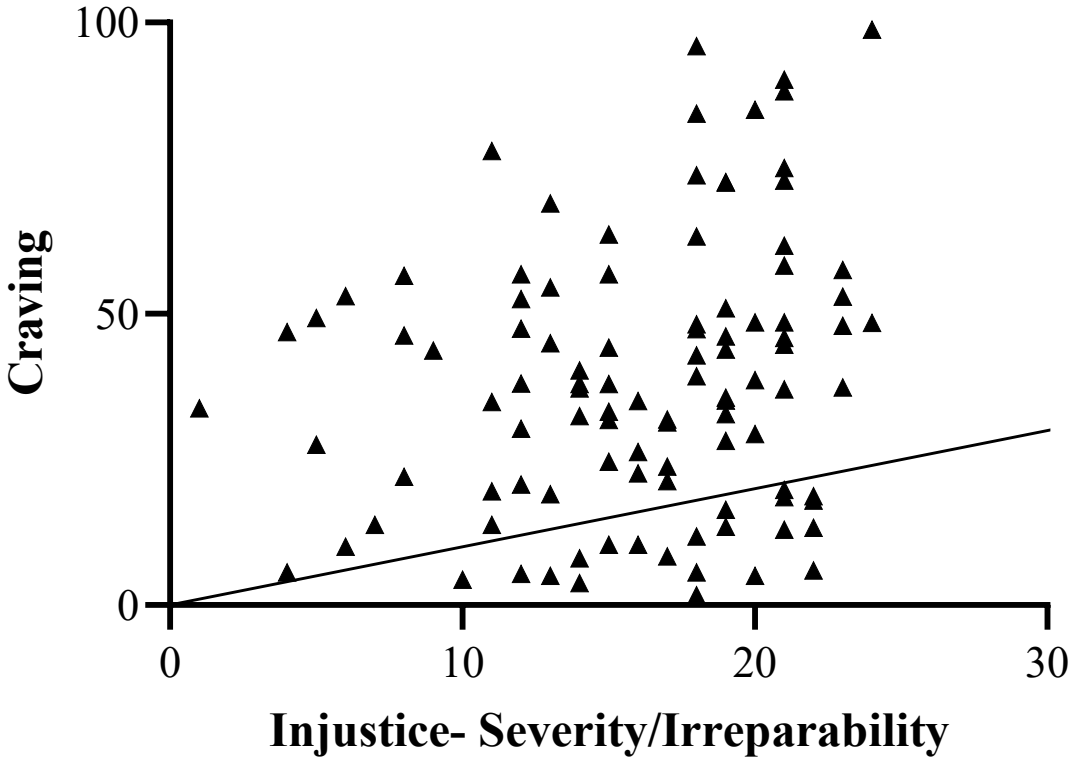
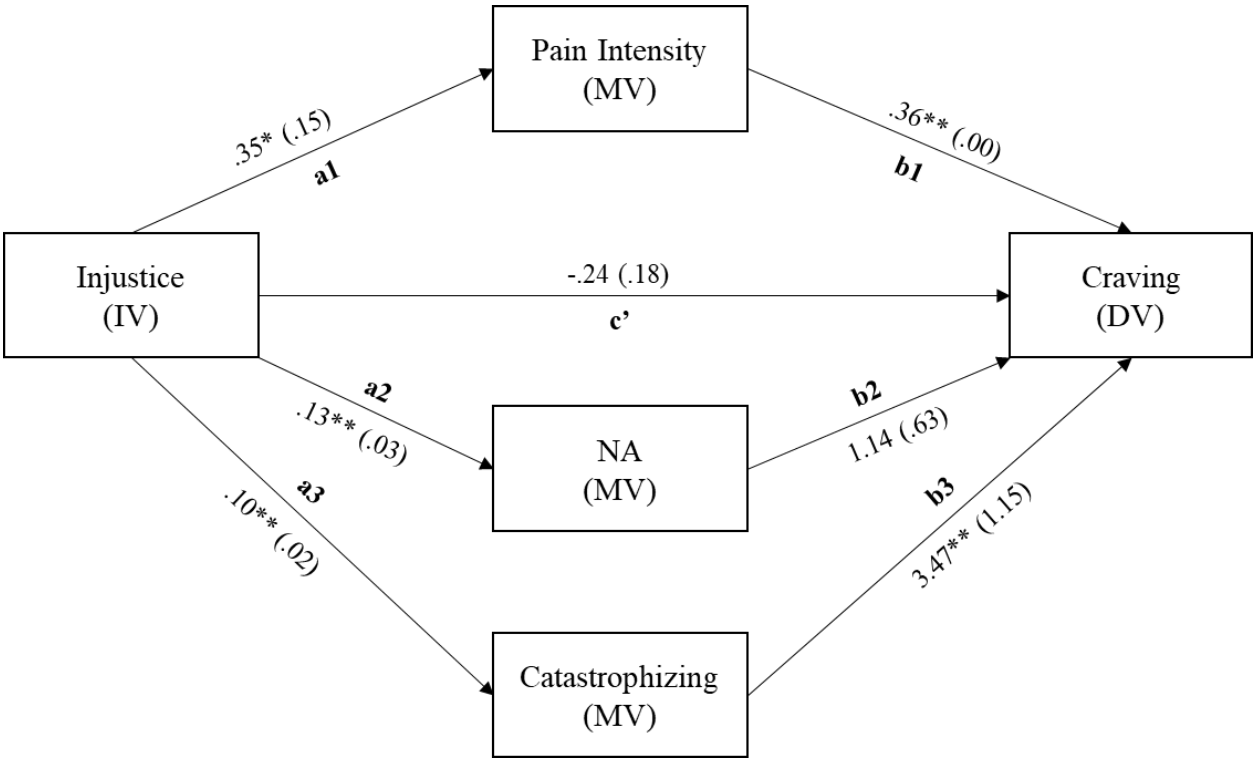


Figure 3
The mediating effect of pain intensity, NA, and catastrophizing in the association between perceived injustice and opioid craving.



Note. Values are unstandardized beta coefficients. Values in parentheses are standard errors. Gender, ethnicity, and past-year substance use problems were included as covariates in the model.

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