CANUE: A Theoretical Model of Pain as an Antecedent for Substance Use

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Abstract

Background Pain and substance use are frequently comorbid and have been shown to exert bidirectional effects. Self-medication of pain and distress via substance use is common and can be understood via negative reinforcement, ultimately strengthening the pathway between pain to substance use over time. As such, a testable model of the potentially modifiable candidate mechanisms that underlie the pain to substance use pathway is needed.

Purpose This review proposes a testable model of pain as an antecedent to substance use to guide future research and inform clinical practice.

Methods An integrative review of current evidence regarding pain, substance use, and associated risk factors (i.e., negative affect, pain-related attitudes, negative urgency, and substance use outcome expectancies) was conducted.

Results The Catastrophizing, Anxiety, Negative Urgency, and Expectancy (CANUE) model highlights modifiable risk factors for self-medicating pain with substance use, including increased negative affect and maladaptive pain-related attitudes (i.e., pain catastrophizing, pain anxiety, and fear of pain), negative urgency, and substance-related outcome expectancies for pain relief and enhanced pain coping.

Conclusions Targeted behavioral and psychological interventions that address these factors may facilitate more adaptive pain-coping responses, thereby reducing the impacts of pain on substance use. Systematic research is needed to evaluate the validity and clinical utility of this model.

Keywords: Pain · Substance use · Alcohol · Cannabis · Nicotine · Opioid use

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Introduction

Chronic pain, which has been defined as pain that persists past the normal time of healing (i.e., 3–6 months), is a growing public health concern [1]. It affects 20% of Americans and accounts for significant physical, psychosocial, and economic burden [2–4]. A growing body of evidence suggests that chronic pain and substance use often co-occur, with prevalence rates for substance use disorder (SUD) among this population estimated to range from 3% to 48% [5–7]. Both chronic pain and substance use exert a significant public health burden, particularly in terms of health care costs, lost productivity, and reduced quality of life, and they likely combine to produce synergistic effects on individuals and health care systems [8–10]. Negative reinforcement (i.e., avoidance of aversive stimuli or alleviation of aversive states) is a central process that has been used to explain the development and maintenance of SUDs across multiple theoretical perspectives [11–13] and is one mechanism that may explain the association between chronic pain and substance use. The self-medication hypothesis further posits that individuals may experience negative reinforcement by attenuating aversive internal states via

direct pharmacological effects of substance use [14]. Existing literature suggests that using alcohol and/or other substances to manage pain-related symptoms and distress is a common behavior consistent across various painful conditions and substances [6, 15–24]. Individuals may come to use substances as a means for coping with pain if they (a) initiate the use of a substance to which they were previously naive, (b) resume the use of a substance from which they had previously been abstinent, or (c) modify or maintain their existing, potentially long-standing patterns of substance use. In all cases, individuals would be expected to maintain or increase their use of substances for pain coping if their aversive internal states are alleviated in the context of substance use. Thus, negative reinforcement and self-medication hypotheses help to explain substance use to cope with the pain experience, which often includes distress, negative affect, and aversive sensory experiences.

For purposes of the current review, we define self-medication of pain as coping with pain by using substances outside of the supervision of a medical provider or in a manner that exceeds providers' prescriptions or recommendations. This definition captures two important concepts: (a) pain as a motivator of substance use and (b) the medical and sociolegal context in which substance use may occur. In the case of alcohol use or tobacco smoking, this interpretation is clearly applicable given that neither is a recognized treatment for pain. We acknowledge there is more nuance in the applicability of this definition in describing opioid or cannabis use. We do not believe that "self-medication" accurately describes the behavior of someone taking an opioid analgesic as prescribed by their physician or dentist. However, the situation with cannabis is substantially muddier given the comparatively lax regulation around its medical use compared to opioid analgesics and wide availability outside the medical context through both licit and illicit channels.

In considering the relationship between chronic pain and substance use, Ditre et al. [8] recently proposed a broad, reciprocal model that described pain–substance use interactions as a positive feedback loop resulting in exacerbation and maintenance of both conditions over time (Fig. 1) [8]. Broadly, the reciprocal model integrates findings from research examining both the effects of substance use on pain and the effects of pain on substance use. Specifically, a limited but growing body of evidence suggests that, for substances, including alcohol, nicotine (tobacco), opioids, and cannabis, pain may be a critical motivator of substance use, increasing the risk of developing SUD and acting as a barrier to cessation and a risk factor for lapse/relapse for those in recovery [25–27]. First, these substances have been shown to provide acute analgesic effects, which, in the short term, is negatively reinforcing [28–30]. However, repeated use to self-manage

Fig. 1. Reciprocal model of pain and substance use. This reciprocal model, as proposed by Ditre et al. [8], details relationships between pain and use of alcohol and other substances. Pain and substance use are hypothesized to interact in a positive feedback loop, resulting in the worsening of both conditions over time. Accordingly, there is a shared vulnerability to chronic pain and addiction among individuals with pain and individuals with substance use disorders. We focus on the relationship between pain and substance use specifically, as pain has been shown to motivate substance use and many individuals with pain endorse substance use for pain coping.

pain and distress may actually contribute to the development and progression of chronic pain, partly as a result of maladaptive plasticity in neural structures and circuits underlying pain and reward processing. Over time, substance use may become a preferred strategy to manage pain and pain-related negative affect, and pain may become a barrier to cessation and/or precipitant of relapse [8, 24, 31]. People who engage in chronic heavy substance use are also likely to experience increased pain or hyperalgesia during periods of abstinence. Indeed, pain and/or hyperalgesia are components of the withdrawal syndrome associated with alcohol [32], nicotine [24, 33], opioids [34], and cannabis [35]. Ultimately, upon becoming a preferred strategy to cope with pain and pain-related distress, substance use may displace more adaptive strategies for the management of pain, such as mindfulness, exercise, activity pacing, and relaxation techniques [8]. In particular, mindfulness training may have utility in providing pain relief, targeting neurocognitive mechanisms associated with SUDs (e.g., increased reactivity to stress and reward process dysfunction), and reducing relapse risk [36–38], Overall, the reciprocal model suggests that there is a shared vulnerability to chronic pain and addiction, and clinical efforts should involve integrated treatments targeting both conditions. In particular, treatments for substance use should consider the putative role of pain in the maintenance and progress of addiction.

Ditre et al. [8] proposed several potential mechanisms underlying the pain to substance use pathway, including pain-related negative affect, expectancy of analgesia, and pain-coping self-efficacy and resilience. An important next step in this area of research is to develop a testable theory of how the large number of candidate factors and constructs may interact to predict the influence of pain on substance use behavior. Given the high prevalence and rates of co-occurrence between pain and substance use,

a focused model that helps to explain how pain serves as an antecedent to substance use is warranted. In addition to previously identified mechanistic constructs, the role of additional putative mechanisms should also be clarified in future studies. For example, the potentially critical role of negative urgency in this model has not been described. Thus, the objective of this review is to propose a specific, testable model for the pain to substance use pathway that could be used to guide future research and inform clinical practice within the context of the larger reciprocal model. Empirical studies in the broad domain of pain and substance use can be usefully dichotomized, by direction of hypothesized causality, into investigations of either effects of substance use on pain or effects of pain on substance use. That is, it is important to distinguish between studies that examine how substance use may produce acute analgesia or serve as a risk factor in the development of chronic pain (i.e., effects of substance use on pain) and those that examine how pain may serve to motivate or maintain substance use (i.e., effects of pain on substance use). Although integrating these two pathways can help to illustrate/conceptualize pain–substance use relations as operating in the manner of a positive feedback loop, it is also critical to note that they are likely driven by direction-specific processes and mechanisms that warrant focused theoretical/empirical explication. We chose to specifically focus on the pain to substance use pathway given evidence that pain can act as a motivator for substance use and pain patients often endorse the use for coping purposes. Understanding of how pain may provoke substance use, as well as related cognitive–behavioral factors, may inform targeted substance use prevention and intervention approaches among those with pain. In particular, we hope that the model may be useful in identifying pain patients at risk of self-medication, a common behavior among people with pain that could result in serious adverse consequences. Additionally, our hope is that clinicians and researchers who specialize in addiction (particularly nonopioid addiction), who may not be routinely considering or addressing pain, may benefit from the model by being more aware of how pain may influence substance use outcomes or response to treatment.

In summary, our goal was not to provide a comprehensive model of all factors implicated in substance use; rather, we aimed to provide a focused model that highlights individual factors that may account for risk of substance use in the context of pain. We also focused specifically on modifiable cognitive and behavioral factors in order to highlight potential intervention targets for health care providers. We note that, although the biopsychosocial context in which the perception of pain occurs in acute versus chronic pain may differ [39–41], we aimed to develop a model capable of describing cognitive and behavioral mechanisms underlying self-medication behavior in either context. Finally, we are aware that many nonmodifiable, contextual factors (e.g., prior substance use and sociodemographic factors) may interact with such cognitive–behavioral mechanisms to predict self-medication of pain. As such, we describe factors that we believe may be most relevant in greater detail when presenting the complete model.

Given the clinical and empirical relevance of negative reinforcement and self-medication in substance use and addiction, our review uses negative reinforcement as a guiding theoretical framework. However, we note that positive reinforcement-related processes associated with the early stages of progression from substance use initiation to development of a use disorder may occur in parallel to this pain-to-substance use pathway [42]. Although Ditre et al. have previously hypothesized that pain may serve as a barrier to tobacco smoking cessation if smokers with chronic pain lack alternative opportunities for positive reinforcement [24], the majority of the extant literature across substances has focused on negative reinforcement pathways. Therefore, we will review relevant literature that examined the pain-to-substance use pathway, drawing especially on research related to psychosocial factors underlying pain and the use of tobacco, alcohol, cannabis, and prescription opioids. Although these substances differ in pharmacokinetic profiles and acute mechanism of action, we considered them together given common dopaminergic effects and effects on the neural reward system [43]. We also believe that similar motives for use (i.e., to relieve pain and associated negative affect) are observed across these substances, providing a strong basis for considering them simultaneously.

Negative Affect as Mediator of Link Between Pain and Substance Use

Negative affect is a well-documented contributor and consequence of both repeated or heavy substance use and chronic pain. Chronic substance use is associated with both risk for and exacerbation of depression, anxiety, stress, anhedonia, and dysphoria, especially as motivations for use shift from primarily positive reinforcing effects of use in the Binge/Intoxication stage to relief of withdrawal symptoms and craving in the Preoccupation/ Anticipation stage [42]. Individuals with these affective conditions are also at elevated risk of developing an SUD [44]. Similarly, chronic pain is associated with manifestations of depression, anxiety, and anger. In fact, 65% of depressed patients report more pain symptoms than the general population [45] and there is a reciprocal correlation of pain and depression severity, with

each increasing if the other worsens. Anxiety is also more prevalent in individuals with chronic pain than the general population [46–48]. Anxiety-prone patients with pain may develop significant distress and disability associated with pain-related fear and catastrophizing, and this negative affect is associated with craving for opioids even where there is no evidence of addiction [49, 50]. Anger is also a prominent, aversive emotion that exacerbates and can be a consequence of pain. Greater anger expression has been consistently associated with elevated pain intensity and poorer functional outcomes [51], and anger has been documented as the most important self-reported feature for classifying individuals with and without fibromyalgia [52]. Further, experimental studies have also identified anger as a risk factor for intensification of pain and reductions in pain threshold and tolerance [53, 54]. Finally, negative affect also plays a central role in the pain experience, which is inherently aversive [55].

Given that negative affect is a critical component of both substance use and pain, it is not surprising that pain-related negative affect has been shown to mediate the effect of pain on subsequent substance use. In treatment-seeking individuals with SUD and alcohol use disorder (AUD) followed for up to a year posttreatment in two large longitudinal studies (the COMBINE and UKATT studies) [56, 57], pain was a potent predictor of drinking lapses posttreatment [58], and pain-related negative affect was shown to significantly mediate the relationship between pain report at treatment discharge and posttreatment drinking behavior [59]. Initial experimental evidence supports these clinical findings. In a laboratory study using heat pain induction following peripheral sensitization via capsaicin application, pain induction significantly increased urge and intention to drink, and this effect was significantly mediated by state negative affect [26]. Negative affect has also been shown to mediate the effect of experimental pain on the urge to smoke and subsequent smoking behavior [25, 27, 60]. Although empirical literature specifically examining the role of pain as an antecedent to substance use is small, it is consistent with a number of studies showing a link between negative affect (not necessarily linked to pain) and substance use outcomes following discharge from treatment (e.g., Witkiewitz and Villarroel [61]).

Because pain appears to provoke substance use, at least partly as a function of negative affect induction, it is important to characterize the biopsychosocial mechanism(s) underlying this link. Moderators of this link have been extensively studied within the pain literature and include a number of both modifiable and nonmodifiable factors. Nonmodifiable moderators include sex [62, 63], genetic factors [64], and race/ethnicity [65], as well as pain location, duration, and strength [15].

Modifiable factors, which are of particular interest in this review given their potential to serve as treatment targets to disrupt pain–substance use links in patients, include pain catastrophizing, pain anxiety, and fear of pain.

Pain catastrophizing is maladaptive cognitive response to pain characterized by high perceived threat from pain and lower perceived ability to tolerate pain. Pain catastrophizing includes helplessness, rumination, and magnification of pain experience [66]. Pain-related anxiety is a maladaptive cognitive–behavioral response that promotes anxious or fearful responses to pain [67]. Fear of pain represents a complementary but distinct construct to pain catastrophizing and pain-related anxiety. People with elevated fear of pain may be compelled to avoid activities that may result in the experience of pain due to the strong negative affective response it provokes (i.e., catastrophizing and anxiety), increasing the risk for chronic pain and associated disability [68–70]. In individuals with chronic pain, greater pain catastrophizing, fear of pain, and pain-related anxiety have been shown to predict greater clinical pain intensity, pain-related functional limitation, and psychological distress [71–74]. Experimental studies involving both individuals with chronic pain and pain-free controls suggest that a greater burden of these factors, especially fear of pain, also predicts more robust pain responses in laboratory-based quantitative sensory testing [75–77]. Taken together, evidence suggests that negative affect has diverse, interrelated manifestations (e.g., anxiety, depression, pain catastrophizing, and anger) that can emerge in acute contexts and/or remain chronic/stable over time. Both acute experiences of negative affect and more chronic negative affective states are likely to play a role in motivating substance use and serve as a barrier to cessation [27, 78–81].

Negative Urgency as a Moderator of the Pain to Substance Use Pathway Mediated by Negative Affect

As described, several studies have demonstrated that negative affect mediates the association between pain and subsequent substance use. However, induction of negative affect alone is likely insufficient to fully explain how pain may act as an antecedent for substance use. We posit that individual differences in response to negative emotional states and feelings of distress may offer additional predictive information above and beyond tendency for pain to produce strong increases in negative affect.

To this point, negative urgency, which is defined as a tendency to act impulsively when distressed, has been associated with a range of negative behaviors, including suicidality, disordered eating, risky sexual behavior, and substance use [82–84]. Negative urgency is one of

the five factors of impulsivity assessed by the Urgency, Premeditation (lack of), Perseverance (lack of), Sensation Seeking, Positive Urgency, Impulsive Behavior Scale (UPPS-P), a widely used and well-validated measure of impulsivity [85]. Other measured UPPS-P traits include premeditation, perseverance, sensation seeking, and positive urgency. Compared to perseverance, sensation seeking, and premeditation, negative and positive urgency place a greater emphasis on emotion as a precursor to impulsive actions. Negative urgency is conceptually distinct from positive urgency, which refers to the tendency to act impulsively when experiencing extremely positive emotion, and is particularly relevant to understanding how pain may provoke self-medication behaviors. Prior research demonstrates that negative urgency also has good discriminant validity compared to other impulsivity traits, such as sensation seeking and lack of planning [86]. Although there is emerging empirical support for the role of positive urgency in substance use [87], negative urgency may be particularly salient for negative reinforcement pathways, as individuals with high negative urgency likely act impulsively to avoid or escape negative emotions. Given our focus on negative reinforcement as a theoretical framework for pain-related self-medication with substances, we will focus on negative urgency for the purposes of this review.

Negative urgency has been found to predict problematic alcohol use [82, 88, 89], tobacco use [90–92], cannabis use [93, 94], and prescription opioid misuse [95]. In a large sample of first-year college students, Kaiser et al. identified negative urgency as a strong predictor of substance use, above and beyond trait negative affect and distress tolerance [96]. Similarly, negative urgency was found to be the impulsivity factor most strongly related to dependence and severity of substance use-related consequences (e.g., medical, work related, and legal) in a sample of individuals with SUDs [97]. Urgency scores alone were also able to discriminate between those meeting criteria for substance dependence and drug-free controls with 83% accuracy, emphasizing the unique importance of negative urgency to understanding SUDs. Elevated negative urgency has been associated with a stronger relationship between substance use and several measures of negative affect among cannabis and alcohol users, including depression, anxiety sensitivity, and anxiety symptomology [98–103].

Findings that negative urgency may moderate the association between negative affect and substance use provide additional evidence that the tendency to act impulsively to relieve distress may be a critical factor in understanding pain as an antecedent for substance use. For instance, negative urgency has been shown to account for the relationship between depressive symptoms and earlier onset of alcohol use among adolescents [103]. Negative urgency has also been found to

moderate the relationship between anhedonia and nicotine dependence [104]. Overall, these observations are consistent with prior literature indicating that that those with high negative urgency may have difficulty coping with negative affect such that it reduces their ability to make adaptive choices, thereby potentially facilitating substance use [82]. Although we are unaware of literature connecting negative urgency with acute or chronic pain or pain negative affect, previously established links between negative affect, negative urgency, and substance use provide a strong rationale to consider the role of negative urgency in pain as an antecedent for substance use as well. Thus, it is plausible that negative urgency may moderate the effect of negative affect on subsequent substance use such that pain-related negative affect may predict substance use to a greater degree among individuals with higher levels of negative urgency (i.e., a moderated–mediator relationship).

Expectancy of Substance-Related Analgesia as a Moderator of Pain to Substance Use Pathway

Outcome expectancies, or beliefs about the consequences of behavior, have long been implicated in cognitive-based theoretical models of addiction and are highly associated with initiation and maintenance of substance use behaviors, including alcohol, tobacco, and cannabis use [105–108]. Outcome expectancies also have strong effects on subjective response to alcohol [109] and other substances [107]. Couched within Social Cognitive Theory, outcome expectancies can be formed by past experiences, are dynamic, and are not dependent on validity in order to influence behavior [110]. Thus, expectancy of positive outcomes, such as relief from pain and pain-related negative affect, may act as a motivator of substance use, while expectancy of negative or unfavorable outcomes may serve as a deterring factor. Of note, route of administration or substance-specific pharmacokinetics may play a role in the formation of positive expectancies by increasing potential for abuse liability in the context of pain self-medication [111–118].

Substantial evidence indicates that individuals who hold more positive expectancies about substances report greater substance use than those who do not [119, 120]. In the context of pain, research has suggested that expectancies may influence the degree to which substance use reduces pain in the short term [8], with acute pain relief potentially strengthening outcome expectancies for the utility of substance use as an effective coping strategy for pain. It has also been demonstrated that manipulating expectancies related to the pain-relieving effects of smoking reduces the effect of laboratory-based pain induction on motivation to smoke cigarettes [60].

Substance-use-specific expectancies for pain relief and enhanced coping have been examined for cannabis and tobacco use. For example, in a sample of perioperative patients, more than 80% believed that cannabis could be at least somewhat effective for the management of pain after surgery [121]. Furthermore, expectancies about relief from menopause symptoms, including joint/muscle discomfort (endorsed by 87% of a sample of menopausal and postmenopausal women), have been found to mediate the relationship between menopause symptoms and frequency of cannabis use such that greater endorsement of positive expectancies was related to increased frequency of use [122]. Similar findings were observed regarding expectancies of cannabis-induced relief from symptoms of premenstrual syndrome and premenstrual dysphoric disorder, including insomnia, irritability, depression, and joint pain [123]. Moreover, results of a preliminary analysis indicate that expectancy of symptom relief moderated the association between total number of symptoms of posttraumatic stress disorder and cannabis use in a group of combat-exposed veterans. More specifically, veterans who reported stronger expectancies of cannabis relief from symptoms of posttraumatic stress disorder, such as intrusions, avoidance, and numbing, consumed more ounces of cannabis per month than those with weaker expectancies [124]. Overall, individuals appear to hold expectancies of cannabis-induced relief for a variety of negative physical and emotional states, and these expectancies are associated with more frequent use patterns of cannabis use, thereby strengthening negative reinforcement pathways.

Commensurate with literature on cannabis expectancies, previous research has demonstrated that experimental pain induction increased smoking urge and behavior, particularly for individuals that hold expectancies that smoking will help reduce pain [125]. Additionally, expectancies of smoking as an effective coping strategy for pain have been prospectively associated with lower odds of smoking abstinence, highlighting the process by which expectancies can also facilitate maintenance of substance use behavior [126]. While these findings have been primarily documented among cannabis and tobacco users, it is likely that they extend to other substances, including alcohol [8, 31] and opioids [127]. Taken together, positive expectancies about substance use likely moderate the effects of pain on substance use such that individuals who hold stronger expectancies that substance use effectively reduces pain severity or pain-related distress may engage in more frequent substance use than those who do not. There is also evidence that substance-related expectancies for analgesia can be successfully manipulated [60], suggesting that this may be an important target for intervention

among those with pain. By the same token, expectancies of short- or long-term negative consequences from substance use (e.g., increased pain over time) could make self-medication behaviors less likely.

Catastrophizing, Anxiety, Negative Urgency, and Expectancy: A Focused Cognitive–Behavioral Model of Pain as an Antecedent of Substance Use

Although the systematic study of pain as an antecedent for substance use has only recently begun, we believe that there is adequate evidence within the disparate literatures regarding psychosocial influences on pain and the use of alcohol, tobacco, cannabis, and opioids to inform the development of a focused cognitive–behavioral model regarding this path. However, to our knowledge, such a model has yet to be proposed. In developing this model, we seek to provide a very granular level of detail in order to generate testable hypotheses and directly inform evidence-based interventions to decrease self-medication behavior and reduce associated SUD risk. Furthermore, we present the Catastrophizing, Anxiety, Negative Urgency, and Expectancy (CANUE) model as a means of improving understanding of cognitive and behavioral risk factors for problematic substance use in the context of pain above and beyond currently well-understood biopsychosocial influences on substance use (i.e., sociodemographics, substance use history, mood disturbance, and mental health history).

It is intuitive to suggest that less severe elevations in state negative affect associated with pain would be less likely to prompt an individual to engage in substance-related self-medication behavior. Attitudes and beliefs about pain, including pain catastrophizing, pain anxiety, and fear of pain, have been shown to moderate the degree to which the experience of pain elevates negative affect. These relationships are well supported by both the psychosocial and pain literature [128] and the existing body of literature regarding negative affect as a mediator in the effects of pain on substance use [26].

However, these factors alone are likely insufficient to explain individual differences in the degree to which pain acts as an antecedent for substance use. Additional factors may be needed to more fully characterize this path. Impulsivity, particularly negative urgency, may be a particularly important consideration. Specifically, negative affect may motivate substance use as a function of negative urgency. In other words, individuals who experience pain-related negative affect but have low negative urgency may be more likely to employ adaptive coping strategies and less likely to use substances in response to pain. However, in the context of higher

negative urgency, substance use may become increasingly relied upon for pain coping without consideration of more adaptive alternatives. Expectancy of pain relief from substance use is likely to be another critical moderating factor. Individuals who do not believe that substance use will meaningfully affect their symptoms, provide relief, or reduce distress may be less likely to self-medicate their pain via substance use. Proposed relationships among these variables are formalized in Fig. 2, which illustrates our conceptual CANUE moderated–mediator model of critical psychosocial factors that may account for individual differences in pain as

an antecedent for substance use. Consistent with existing literature, the CANUE model proposes that pain acts indirectly to provoke substance use by increasing negative affect. Individual differences in pain attitudes, including pain catastrophizing, pain anxiety, and fear of pain, may moderate the effect of pain on negative affect. Negative urgency, in turn, may moderate the effect of negative affect on subsequent substance use. Finally, substance-related outcome expectancies for pain relief and enhanced pain coping may moderate the relationship between pain and substance use. Thus, in the CANUE model, the cluster of cognitive and behavioral
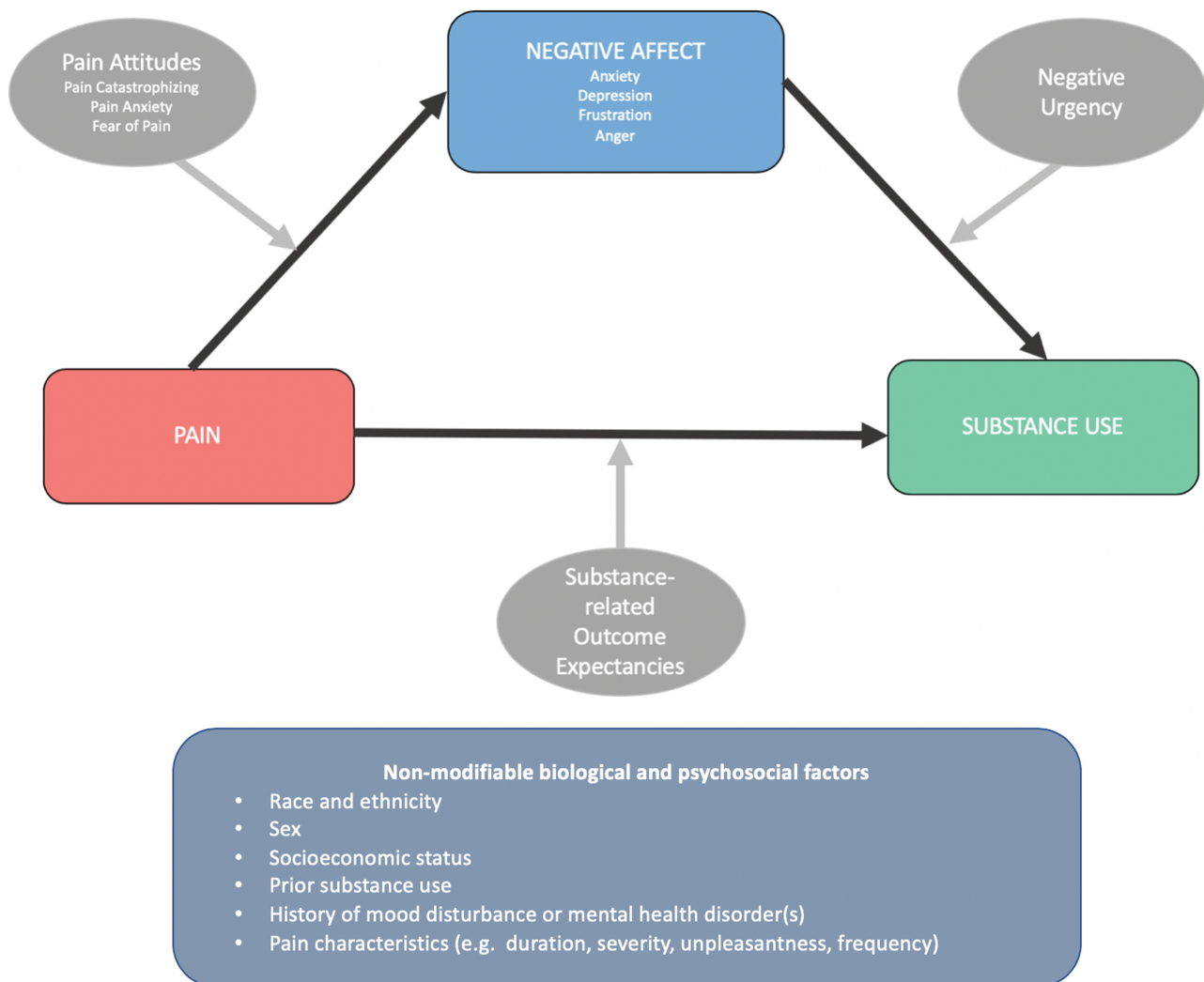

Fig. 2. Catastrophizing, Anxiety, Negative Urgency, and Expectancy (CANUE) model of pain as an antecedent to substance use. This model integrates current findings examining the effect of pain on substance use for self-medication purposes. In line with previous literature, we propose that pain acts indirectly to provoke substance use by increasing negative affect. Individual differences in pain attitudes, including pain catastrophizing, pain anxiety, and fear of pain, may moderate the effect of pain on negative affect. Negative urgency, in turn, may moderate the effect of negative affect on subsequent substance use. Finally, substance-related outcome expectancies for pain relief and enhanced pain coping may moderate the relationship between pain and substance use. Together, we propose that increased negative affect and maladaptive pain-related attitudes (i.e., pain catastrophizing, pain anxiety, and fear of pain) and negative urgency in the context of strong substance-related outcome expectancies for pain relief and enhanced pain coping may confer the greatest risk for self-medication with substances among those with pain. This should be considered within the context of nonmodifiable factors, including sex, race, ethnicity, socioeconomic status, prior substance use, history of mood disturbance or mental health disorder(s), and pain characteristics, all of which may affect factors included within the model.

characteristics that may be seen as a "perfect storm" for increased risk of engaging in self-medication of pain include high levels of pain catastrophizing, pain anxiety, fear of pain, pain-related negative affect, negative urgency, and expectancy that a given substance will provide relief, as well as low expectancy of negative consequences from using a given substance. Reducing some or all of these moderating factors using targeted behavioral and psychological interventions (e.g., reducing pain catastrophizing/negative urgency and challenging expectancies for substance-related pain relief) could disrupt this path by reducing pain-related negative affect and allowing a patient the opportunity to pursue more adaptive coping strategies, resulting in meaningful reductions in the risk of substance use among individuals with pain.

We had several goals in elaborating this moderated–mediator model of pain as an antecedent for substance use. We determined that the model should be both testable and falsifiable. As proposed, the validity of the model can be tested either in parts or as a whole. One can envision many potential experimental designs in the context of both experimental and clinical pain to evaluate the proposed relationships. We also aimed to develop a model with strong predictive utility that may enable researchers and clinicians to identify individuals at high risk for engaging in self-medication of pain via substance use. Importantly, each moderator proposed in our model is modifiable, suggesting that they could be valuable treatment targets to mitigate the risk of developing or maintaining an SUD among individuals with pain. While many factors contribute to the development and continuation of substance misuse (e.g., substance use history and genetic risk factors), this model highlights the role of modifiable cognitive–behavioral factors that may serve as targeted intervention points. Furthermore, in principle, a screening tool could be developed to facilitate the assessment of each of the identified risk domains (negative attitudes about pain, negative urgency, and substance-specific expectancies of pain relief). Such a tool could be readily employed in clinical settings and would allow clinicians to direct high-risk patients for individualized psychological and/or behavioral treatments targeting these processes, thereby potentially reducing the likelihood of further problematic substance use. A challenge to this approach is that existing assessments for constructs of interest are quite lengthy and may not be practical for clinical use. However, an abbreviated tool could be developed by administering full-length questionnaires assessing each domain and determining an optimal reduced item set that most accurately predicts those scores in the upper quartile. Similar approaches have shown promise for identifying acute and subacute low back pain patients at high risk for developing chronic pain [129].

Utility of the CANUE Model to Improve Mechanistic Understanding of Nonmodifiable Risk Factors for Self-Medication

The CANUE model may also provide a useful mechanistic framework for understanding how nonmodifiable biological and psychosocial factors may modulate the risk of engaging in potentially hazardous self-medication behavior. For instance, Riley and King [15] found that men were approximately twice as likely to self-medicate orofacial or arthritis pain with alcohol relative to women. Although the mechanism underlying this effect was unclear, subsequent studies have suggested that the relationship between pain-related anxiety and alcohol- and opioid-related consequences are stronger among men than women [78, 81]. Other mechanisms may contribute to sex differences in self-medication as well. It is possible, for example, that differences in the expectancy of pain relief and/or negative consequences from alcohol use may have accounted for elevated risk of self-medication behavior among men. Racial and ethnic differences in self-medication behavior (i.e., lower likelihood of self-medication among Black and/or Hispanic/Latinx individuals compared to White and/or non-Hispanic/Latinx individuals) may also be better understood in the context of the CANUE model [15]. Additionally, pain characteristics (e.g. duration, frequency, severity, and unpleasantness) may be useful to consider within the CANUE model. Greater pain frequency and longer pain duration have been associated with alcohol use for self-medication of orofacial and arthritis pain [15], while greater pain unpleasantness and severity have been linked to motivation to use alcohol [130], greater frequency of cannabis use [131], and risk of opioid misuse [132]. These characteristics may interact with those identified in the CANUE model to predict the likelihood of self-medication of pain with substances such that more frequent, intense, long-lasting, and unpleasant pain may be associated with elevated negative affect and subsequent risk of self-medication.

The CANUE model should also be considered in the context of an individual's substance use history. It is possible that many individuals with pain have had exposure to various substances (e.g., tobacco, cannabis, opioids, and alcohol) before the onset of their pain. Prior substance use may directly impact certain cognitive–behavioral factors in the model, particularly expectancies of pain relief, modulating likelihood of self-medication following pain onset. It may also contribute to the development of pain itself [8]. Similarly, factors in the CANUE model may be affected by a history of mood disturbance or mental health disorder(s). Specifically, prior mental health concerns, such as depression or anxiety, may predispose an individual toward maladaptive pain-related

attitudes (e.g., pain catastrophizing and fear of pain), increased pain-related negative affect and negative urgency, and, indirectly, greater risk of substance use subsequent to pain.

We highlight several nonmodifiable biological and psychosocial risk factors for self-medication of pain (e.g., sex, race, ethnicity, socioeconomic status, prior substance use, history of mood disturbance or mental health disorder(s), and pain characteristics) that may meaningfully influence components of the CANUE model in Fig. 2.

Clinical Implications of the CANUE Model

The CANUE model highlights the role of potentially modifiable cognitive–behavioral constructs in pain–substance use relations, with direct implications for assessment and treatment of substance use in the context of pain. First, clinicians should be aware that pain may serve as a proximal motivator of acute bouts of substance use and that over time, substance users in pain may increasingly rely on substance use as a primary strategy for coping with pain. When working with patients who present with substance use concerns, clinicians should assess both pain (e.g., numeric or visual analog rating scales with consistent anchors) and perceived interrelations between pain and substance use (e.g., expectancies for analgesia) [133]. It may also be helpful for clinicians to assess both substance use and mental health history in order to develop a richer understanding of how their patients' prior experiences may interact with CANUE-related factors and current substance use patterns, as well as to inform the development of tailored treatment recommendations. Overall, the CANUE model highlights the potentially critical roles of pain-related fear, negative urgency, and substance-related outcome expectancies in interrelations between pain and substance use. Therefore, clinicians should consider brief assessments for these constructs to inform treatment planning. As previously noted, development and validation of a brief but comprehensive screening tool assessing CANUE domains may have particular utility in this regard. Interventions should incorporate specific elements of cognitive behavioral therapy, acceptance and commitment therapy, mindfulness-oriented recovery enhancement, and dialectical behavior therapy to address elevated CANUE domains, as these have been found to be successful in targeting pain and substance use concurrently [134–136].

Patients who present with high levels of pain-related fear (e.g., pain catastrophizing, fear of pain, and pain-related anxiety) may be candidates for cognitive–behavioral treatments that intervene on these maladaptive pain responses [136]. For example, cognitive restructuring can be used to modify maladaptive pain-related cognitions inherent in catastrophic thinking and pain-related anxiety. Behavioral techniques, including exposure, can be used to target maladaptive behavioral responses (e.g., avoidance of pain-provoking stimuli), and relaxation techniques may also be helpful for reducing physiological arousal. In the context of the CANUE model, interventions designed to decrease fear of pain would place particular emphasis on regulating pain-related negative affect. Ongoing assessment during the course of treatment would then focus not only on changes in pain-related fear but also on subsequent levels of negative affect. Treatment may be augmented with emotion regulation strategies and distress tolerance skills training that seek to help patients decrease and manage negative affective states [137, 138].

The CANUE model further proposes that patients may be more susceptible to the effects of pain on substance use via negative affect if they present with high levels of negative urgency. Patients with high negative urgency may increasingly resort to substance use as a primary coping strategy for pain-related negative affect without consideration of alternative, more adaptive behaviors. To the extent that substance use is readily available and negatively reinforcing, the pain-to-substance use pathway may strengthen over time, thus impairing efforts to reduce or quit substance use and precluding the development of alternative pain-coping strategies. Several cognitive–behavioral and mindfulness-based approaches may have utility for reducing negative urgency and providing additional opportunity for patients to more consistently use adaptive coping strategies. For example, stimulus control techniques seek to limit exposure to triggers, while response prevention introduces alternative or compensatory behaviors [139]. Mindfulness techniques can assist patients in observing impulses without acting on them and provide an opportunity to then engage alternative coping strategies and cognitive restructuring [137]. In particular, mindfulness-based interventions have been associated with reduction of pain and treatment of SUDs [36–38], which suggests promise in intervention for self-medication behaviors.

Patients who hold or come to develop stronger substance-related expectancies for analgesia and pain relief may engage in substance use more consistently than those who do not, leading to substance use becoming a preferred coping strategy for pain. Expectancies of pain relief from smoking have been successfully challenged [60] and may be an important target for intervention among those with pain. In this study, expectancies were manipulated by presenting a video with information about the associations between smoking and pain (e.g., the relationship between smoking and development and progression of pain) and testimonials

that smoking is not an effective treatment for pain [60]. A similar psychoeducational approach coupled with training in previously mentioned adaptive coping strategies, such as mindfulness or distress tolerance training, may be beneficial to consider within the context of the CANUE model. Interventions should focus on reducing positive expectancies of substance use-related pain relief and strengthening expectancies of short- or long-term negative consequences from substance use (e.g., increased pain and greater risk of developing chronic pain). Taken together, psychological treatments for comorbid pain and substance use may benefit from viewing substance use as a maladaptive behavioral response to the pain experience. As such, more adaptive responses and coping strategies should be introduced as alternatives to substance use. Future research should also consider the role of medication-assisted therapies (e.g., maintenance therapy for opioid use disorder, [extended release] naltrexone for AUD, and nicotine replacement therapy for nicotine dependence) in addition to the psychological interventions proposed given that they may influence CANUE factors (e.g., substance use outcome expectancies) and subsequent patterns of substance use.

Summary

An expansive and established empirical literature substantiates the roles of negative reinforcement and self-medication in the onset and progression of substance-related disorders. More recently, the experience of pain and related cognitive–affective processes (e.g., fear of pain, pain anxiety, and catastrophizing) have been identified as potent motivators of substance use and impediments to abstinence/cessation. The goal of this review was to propose a testable mechanistic model of pain as an antecedent to substance use that may guide future research and inform clinical practice. The resulting CANUE model highlights several modifiable risk factors for engaging in self-medication of pain via substance use, including high levels of pain catastrophizing, fear of pain, and pain anxiety, exaggerated pain-related negative affect, high levels of negative urgency, and strong substance-related outcome expectancies (e.g., for pain reduction/coping). We contend that addressing these conceptualized moderating factors via targeted behavioral and psychological intervention may help to disrupt the pain-to-substance use pathway and support the establishment of more adaptive pain-coping responses. It is our hope that future research will systematically evaluate the relative contribution and clinical utility of the CANUE model in the context of co-occurring pain and substance use.

Compliance with Ethical Standards

Authors' Statement of Conflict of Interest and Adherence to Ethical Standards All of the listed authors declare that they have no conflicts of interests.

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