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Abstract

Benzodiazepines (BZDs), a class of sedative-hypnotic drugs, are at the center of an emerging prescription drug crisis. From approximately 1995-2015, overdose deaths involving BZDs quadrupled and average dose equivalents more than tripled. Specific concern has centered on elevated rates of BZD use among individuals with chronic pain, given that BZDs are generally not indicated for pain management. Consistent with negative reinforcement and motivational models of substance use, desire for pain alleviation may be a salient motivator of BZD use, particularly as individuals commonly report using BZDs for negative affect alleviation. The present study tested cross-sectional associations between pain intensity and clinically relevant BZD use patterns among individuals with chronic pain. We also examined the role of pain catastrophizing, a malleable transdiagnostic factor reflecting negative cognitive-affective pain responses. Participants were 306 adults (M_{age} = 38.7, 38.9% female) with chronic musculoskeletal pain and a current BZD prescription who completed an online survey study via Amazon Mechanical Turk. Hierarchical linear regression results indicated that pain intensity was positively associated with past-month BZD use frequency and BZD dependence severity. Logistic regression results indicated that greater pain intensity was associated with a 1.2 times greater likelihood of endorsing BZD misuse behaviors. Pain catastrophizing was positively associated with BZD dependence severity and likelihood of BZD misuse, after accounting for pain intensity. Initial findings implicate pain/pain-related cognitive-affective processes in higher-risk BZD use, and suggest pain relief is a common, yet underrecognized, self-reported motivation for taking BZDs. Future research should examine mechanisms underlying pain-BZD covariation and co-use behaviors.

Keywords: chronic pain, benzodiazepines

Benzodiazepine Use and Dependence in Relation to Chronic Pain Intensity and Pain Catastrophizing

by

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B.A., Dartmouth College, 2016

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Benzodiazepine Use and Dependence in Relation to Chronic Pain Intensity and Pain Catastrophizing

Benzodiazepines (BZDs), a class of sedative-hypnotic drugs, represent one of the most commonly prescribed medication types (Ashton, 2005; Guina & Merrill, 2018), with up to 13% of adults in the United States reporting past-year BZD use (Blanco et al., 2018; Maust et al., 2019; Olfson et al., 2015). BZDs produce anxiolytic, hypnotic, and muscle-relaxing effects through their action on gamma-aminobutyric acid (GABA) receptor A (Griffin et al., 2013). While insomnia and anxiety remain the most common indications for BZD prescription (Guina & Merrill, 2018), clinical guidelines advise only short-term BZD use for insomnia (Schutte-Rodin et al., 2008) and recommend alternative first-line treatments for anxiety disorders (Bandelow et al., 2014; Bandelow et al., 2017), with more recent changes in guidelines driven by growing recognition of harms associated with BZDs (Bandelow et al., 2017).

BZD use has been termed an emerging epidemic and prescription drug crisis, with addiction experts drawing parallels with the early days of the opioid epidemic (e.g., Lembke et al., 2018; Limandri, 2018). Several trends suggest a growing problem and a need for action. For example, overdose deaths involving BZDs quadrupled from the mid 1990s to 2013 (Bachhuber et al., 2016). During approximately the same period, physician visits involving BZD prescription doubled (Agarwal & Landon, 2019), average dose equivalents more than tripled (Bachhuber et al., 2016), and numbers of continuing prescriptions (i.e., refills) increased (Kaufmann et al., 2018). Recent estimates suggest that among adults reporting any past-year use of BZDs, 17% endorse misuse (i.e., use in any manner not recommended by a physician) and 1.5% meet criteria for BZD-related substance use disorder (Blanco et al., 2018). With growing recognition of the risks and abuse potential of BZDs (e.g., Agarwal & Landon, 2019; Lembke et al., 2018; Votaw

et al., 2019), there is a call to curb overprescription (Lembke et al., 2018) and elucidate biopsychosocial factors contributing to BZD overuse and misuse (Rigg & Ford, 2014). To inform both health policy and professional practice, it is critical to gather data on higher-risk BZD use patterns including heavier use, misuse behaviors, and dependence (Brandt et al., 2018), and to examine populations at particular risk for deleterious effects due to BZD use (e.g., chronic pain; Guina & Merrill, 2018; Pergolizzi & LeQuang, 2020).

Patterns of BZD Use

BZD Misuse

BZDs are the third most commonly misused prescription or illicit substance in the United States (Johnston et al., 2018), with approximately 17% of adults who report any past-year BZD use also reporting misuse (Blanco et al., 2018). Prescription drug misuse may be defined as any use without a prescription or in another way not as directed by a physician, commonly: with a greater frequency, dose, or duration than prescribed (e.g., McCabe, 2005; Votaw et al., 2020). Misuse encompasses several behaviors that increase risk for overdose (e.g., Jones et al., 2012), including taking doses larger than recommended, as well as co-ingestion with opioids, alcohol, or other substances contraindicated in the context of BZD use (Votaw et al., 2019). Additionally, misuse can encompass use over longer time periods than prescribed, which is concerning due to associations of longer-term BZD use with deleterious health outcomes (Ashton, 2005; Guina & Merrill, 2018; Michelini et al., 1996), and because there is no evidence for long-term effectiveness of BZDs even in conditions for which they have demonstrated shorter-term efficacy (i.e., panic disorder, generalized anxiety disorder, social anxiety disorder, insomnia; Guina & Merrill, 2018).

BZD Dependence and Substance-Related Disorders

Individuals prescribed BZDs may develop BZD tolerance (i.e., increasing amounts needed to achieve the same effect, or diminishing effects), physical dependence, and substance-related disorders (Soyka, 2017). Diagnostic and Statistical Manual, Fifth Edition (DSM-5) criteria for Sedative, Hypnotic, or Anxiolytic Use Disorder (SHA use disorder; the category under which BZD use disorders fall) include tolerance/dose escalation, craving, withdrawal symptoms (e.g., acute anxiety, perceptual distortions, insomnia; Ashton, 2005), and continued use despite persistent use-related problems (American Psychiatric Association, 2013). As with other substance use disorders, diagnosis requires two of eleven symptoms and significant distress and/or impairment. Recent estimates indicate that 1.5% of individuals reporting any past-year BZD use also meet criteria for BZD-related SHA use disorder (2015-2016 National Survey on Drug Use and Health; Blanco et al., 2018). Risk for BZD dependence and potential to develop substance-related disorders are thought to increase in the context of frequent and longer-term use (e.g., Soyka, 2017).

BZD Use Frequency

Taking BZDs at higher frequency (e.g., daily versus less than daily) is considered an important indicator of higher-risk BZD use (e.g., Lembke et al., 2018; Votaw et al., 2019). Greater frequency of prescription BZD use has been associated with greater likelihood of misuse (McCabe et al., 2011) and maintenance of use over long-term follow-up (e.g., 3 years, 13 years; Barnas et al., 1993; Isacson, 1997). Several prior studies have used retrospective recall of use frequency over a given time period (e.g., past-month) as an indicator of high-risk use frequency (Dublin et al., 2011; Holm et al., 2012; Nattala et al., 2011), and past-month days of use has reliably been used to index current BZD use frequency (e.g., McHugh et al., 2017; Stein et al., 2016).

Chronic Pain and BZD Use

Chronic Pain Prevalence and Impact

Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (Raja et al., 2020). Chronic pain, (i.e., pain persisting beyond expected healing time or > 3 months; Institute of Medicine, 2011; Treede et al., 2015) affects approximately 50 million adults in the United States, with 20 million reporting pain that frequently interferes with daily activities (Dahlhamer et al., 2018). Musculoskeletal pain (i.e., pain affecting bones, joints, muscles, or ligaments/tendons; Arendt-Nielsen et al., 2011) accounts for the greatest proportion of persistent pain and related disability (Badley et al., 1994; Briggs et al., 2018; Yelin et al., 2014). Pain is a leading cause of lost quality of life (Boonstra et al., 2013; Gureje et al., 1998; Phillips, 2009) and is associated with greater burdens of depression, insomnia, and cardiovascular disease (Fayaz et al., 2016; Goesling et al., 2013; Herrero Babiloni et al., 2020) as well as increased mortality (Smith et al., 2018). Chronic pain engenders substantial economic impact, costing over $250 billion in annual medical expenses and more than $300 billion in lost productivity in the United States (Gaskin & Richard, 2012). Increasingly, scholars favor examination of pain as a multidimensional construct including both pain intensity and pain-related disability (e.g., Turk & Melzack, 2011), since intensity and disability tend to display only moderate correlations with each other (Schmidt et al., 2010; Von Korff et al., 1992), and have demonstrated differential associations with health-related outcomes (e.g., healthcare utilization, presence of substance use disorders, depression/anxiety; Bean et al., 2014; Day & Thorn, 2010; Häuser et al., 2014; McDermott et al., 2018).

BZD Use in Chronic Pain: Prevalence and Impact

Patterns of BZD use among individuals with chronic pain have generated substantial concern among researchers and clinicians (Guina & Merrill, 2018; Pergolizzi & LeQuang, 2020), with commensurate calls for additional research aimed at the explication of biopsychosocial factors contributing to the maintenance and escalation of BZD use in pain populations. Individuals with chronic pain represent a group at higher risk for BZD-related problems for several reasons. First, treatment-seeking chronic pain samples may be 2-3 times as likely as individuals in the general population to report BZD use (over 30% versus 5 - 15%; Agarwal & Landon, 2019; Cunningham et al., 2017b; King & Strain, 1990; Nielsen et al., 2015) and to meet criteria for BZD-related substance use disorder (e.g., Liebschutz et al., 2010). Among chronic pain samples, greater pain intensity has been associated with a greater likelihood of endorsing past-year (Torrance et al., 2018), past-month (Nielsen et al., 2015), and current BZD use (Cunningham et al., 2017b), as well as misuse (Anagnostopoulos et al., 2018). Second, although BZDs continue to be prescribed in the context of pain management (Agarwal & Landon, 2019; Kim et al., 2018; Larochelle et al., 2015) following early work recommending BZDs to treat affective components of pain (e.g., Dellemijn & Fields, 1994), evidence regarding BZD efficacy in the vast majority of pain conditions is lacking (Wright, 2020).

Third, approximately 40% of individuals prescribed opioid analgesics also use BZDs (Gudin et al., 2013), and such co-use is associated with increased risk of overdose and overdose fatality via respiratory depression (Jeffery et al., 2019; Pergolizzi & LeQuang, 2020; Sun et al., 2017). Indeed, risk of opioid-related overdose death may be ten-fold higher for patients also prescribed a BZD (Dasgupta et al., 2016). Finally, it has been argued that management of chronic pain and comorbid symptoms using BZDs may contribute to use without a plan or

impetus for discontinuation (Pergolizzi & LeQuang, 2020), thus increasing the potential for misuse.

Theoretical Perspectives Relevant to Pain-BZD Relations

An established reciprocal model suggests that pain and substance use interact in a bidirectional manner, resulting in the maintenance and exacerbation of both conditions over time (Ditre et al., 2019). Consistent with negative reinforcement (Baker et al., 2004) and self-medication (Khantzian, 1997) paradigms that posit substance use is largely motivated by the desire to ameliorate or escape aversive internal states, pain has been shown to be a potent situational motivator of substance use (e.g., tobacco and alcohol; Ditre & Brandon, 2008; Ditre et al., 2010; Moskal et al., 2018). Accordingly, substance use in the context of pain may be reinforced via negative affect reduction, acute substance-related analgesia, and alleviation of abstinence-induced hyperalgesia (Ditre et al., 2019).

Alleviation of negative affect also appears to play a central role in BZD use (Cox & Klinger, 1988). Broadly, motivational models posit that decision-making is driven by consideration of the net affective consequences of engaging in a given behavior, and *motives* may be understood as the reasons for engaging in a given behavior (Ikard et al., 1969). Coping motives (i.e., using a substance to reduce or cope with negative emotions) are among the most commonly endorsed reasons for BZD use (Boyd et al., 2015; Fatséas et al., 2009; Kokkevi et al., 2008; McCabe et al., 2009; McCabe & Cranford, 2012; McHugh et al., 2017; Vogel et al., 2013; Votaw et al., 2019). Individuals also report using BZDs for somatic self-treatment motives, such as alleviating symptoms of withdrawal from other substances (Messina et al., 2016; Vogel et al., 2013). BZDs are commonly used in combination with opioids or opioid agonist medications (e.g., methadone) to augment their effects, including pain relief (Dwyer, 2008; Hayashi et al.,

2013; Lankenau et al., 2012; Mateu-Gelabert et al., 2017; Motta-Ochoa et al., 2017). Importantly, many patients have reported receiving BZD prescriptions for chronic or post-surgical pain (Parr et al., 2006; Sirdifield et al., 2017) and for insomnia secondary to or exacerbated by pain (Liebrenz et al., 2015; Sirdifield et al., 2017; Williams et al., 2016). Taken together, this literature suggests that desire for pain alleviation is likely a salient motivator of BZD use.

The Potential Role of Pain Catastrophizing in BZD-Pain Relations

To inform interventions for BZD use/dependence in the context of chronic pain, a critical next step is identification of modifiable cognitive-affective factors that underlie pain-substance use relations (i.e., transdiagnostic factors). One such factor is pain catastrophizing, understood as a set of exaggerated, negative, cognitive-affective response styles or schemas related to pain (e.g., ruminating on pain; Campbell et al., 2015; Edwards et al., 2011; Quartana et al., 2009). Pain catastrophizing has been proposed as a key transdiagnostic factor underlying comorbid pain and substance use (Ditre et al., 2019). Pain catastrophizing has been associated with greater fear/worry about pain (Edwards et al., 2011; Quartana et al., 2009) and heightened anxiety during pain induction (McHugh et al., 2020a) and, importantly, pain-related fear may increase propensity to engage in escape/avoidance behaviors in response to pain, including substance use (e.g., McCracken et al., 1992). Empirically, pain catastrophizing has been implicated in pain-driven urge to use tobacco (Kosiba et al., 2018) and use of cannabis for pain-coping (Sterniczuk & Whelan, 2016), and has been associated with greater risk of alcohol dependence (Ciccone et al., 2010) and opioid misuse among individuals with chronic pain (e.g., Martel et al., 2013; Morasco et al., 2013). Pain catastrophizing has also been shown to account for variance in opioid/alcohol craving beyond that explained by pain severity (Kneeland et al., 2019), and in

opioid misuse even after accounting for pain severity, anxiety, and depressive symptoms (Martel et al., 2013). We are aware of only one prior study examining pain catastrophizing in relation to BZD use, and results indicated a positive association between pain catastrophizing and likelihood of BZD use (versus non-use) among 847 treatment-seeking pain patients (Cunningham et al., 2017b).

The Present Study

In addressing a growing crisis regarding BZD use that has disproportionate impact on chronic pain populations, critical next steps include elucidating the relationships of pain with more granular, clinically relevant BZD use patterns (e.g., misuse, use frequency, and dependence) as well as identification of potentially modifiable transdiagnostic factors underlying pain and BZD use. The primary goal of the current study was to test whether pain intensity and pain-related disability are associated with BZD misuse, severity of dependence, and past-month BZD use frequency, among individuals who report a current BZD prescription and chronic musculoskeletal pain. We hypothesized that greater pain intensity and pain-related disability would be associated with greater past-month BZD use frequency, dependence symptoms, and likelihood of BZD misuse. Given evidence that pain catastrophizing may play an important role in pain-substance relations generally (e.g., Kneeland et al., 2019; Kosiba et al., 2018; Sterniczuk & Whelan, 2016) and emerging evidence of correlations with BZD use (Cunningham et al., 2017b), a secondary goal of this study was to examine the role of pain catastrophizing in BZD use frequency/misuse/dependence, including as a potential moderator of hypothesized pain-BZD relations. Specifically, we hypothesized that individuals scoring higher on a measure of pain catastrophizing would display a) greater BZD use frequency, dependence, and likelihood of misuse, and b) stronger relationships of pain with BZD use outcomes.

Method

Participants and Recruitment

Participants were screened for the following inclusion criteria: ≥ 18 years of age, current prescription for one or more BZD medications (i.e., prescription sedatives and prescription hypnotics; Substance Abuse and Mental Health Services Administration, 2018), current chronic musculoskeletal pain, residence in the United States, and ability to read English (see Figure 1 for participant flow chart).

Participants were recruited during March and April 2021 using the crowdsourcing platform Amazon Mechanical Turk (mTurk), a growing source of health sciences and addictions research data (Strickland & Stoops, 2019). First, a human intelligence task (HIT) was posted describing survey content ("You will be asked to answer questions about your health and behaviors."), duration (~1-2 minute screening followed by ~20-35 minute survey), and compensation ($3-$4). Consistent with prior work, access was limited to workers with U.S. residence (Cunningham et al., 2017a; Huhn et al., 2018; Strickland et al., 2019b; Strickland & Stoops, 2015). Next, prospective participants completed a two-part screening procedure designed to mask the intent of the study and eligibility criteria, and thereby minimize deceptive responding (Chandler & Shapiro, 2016; Strickland & Stoops, 2019). Consistent with best practices (Boehnke et al., 2021; Dunn et al., 2016; Huhn et al., 2018; Strickland & Stoops, 2019), a screening questionnaire was completed that contained items of interest for inclusion as well as 'distractor questions' unrelated to inclusion (Appendix E). Part I of the screener assessed age, U.S. residence, ability to read English, and presence of chronic pain, and asked respondents to endorse medications prescribed for them, with response options including "anxiety medications or tranquilizers" and "sleeping medications" in addition to commonly prescribed medications not

of interest for the study (e.g., blood pressure, thyroid, and cholesterol medications; Agency for Healthcare Research and Quality, 2018). Provisionally eligible participants (i.e., those endorsing age ≥ 18 years, U.S. residence, English literacy, chronic pain, and prescription of an anxiety medication/tranquilizer and/or sleeping medication) then advanced to the next page of the screener.

Part II of the screener (Appendix E) was designed to verify the musculoskeletal nature of chronic pain and receipt of a BZD anxiolytic and/or hypnotic. Participants were asked to report their primary location of chronic pain, and those marking "fibromyalgia and/or widespread pain" were excluded, given that differential processes are thought to underlie centralized versus localized musculoskeletal pain (e.g., Arendt-Nielsen et al., 2011). Participants were asked to endorse any medications currently prescribed to them from a list of BZD medications, as assessed by NSDUH 2018. In order to minimize response bias, response options also included non-BZD anxiolytics and hypnotics (e.g., eszopiclone, cyclobenzaprine), "None of the above," and "Not Sure/Don't Know."

Eligible participants then completed a brief (~25-minute) survey. All participants who completed the full survey were compensated regardless of subsequent data exclusions. Consistent with prior work (Beymer et al., 2018; Chandler & Shapiro, 2016; LaRowe et al., 2021; Ruchensky et al., 2018; Strickland et al., 2019a; Strickland & Stoops, 2015, 2017) and an estimated survey completion time of 25 minutes, survey respondents were compensated $3.00-4.00[1].

Online Survey

[1] The first 55 participants were compensated $3 and compensation was raised to $4 for the remaining participants due to concerns about recruitment feasibility.

Additional measures were taken to address two key challenges of crowdsourced data: insufficient effort responding (IER) and deceptive responding. IER may be defined as a response set in which a participant completes survey measures with "low or little motivation to comply with the survey instructions, correctly interpret item content, and provide accurate responses" (Huang et al., 2012). Deceptive or disingenuous responding may involve endorsing behaviors in order to qualify for a study one may not otherwise qualify for (e.g., by exaggerating current or past substance use; Strickland & Stoops, 2019). Given that crowdsourced data precludes biological verification of substance use, efforts to minimize disingenuous responding are critical for use of crowdsourced data in addiction sciences (Black et al., 2019; Strickland & Stoops, 2019).

Incentives for deceptive responding result when participants can discern the purpose of a study and the items or responses upon which inclusion (and thus, payment) is contingent. Accumulating evidence suggests that deceptive responding is more likely when eligibility criteria are known to participants (e.g., Chandler & Paolacci, 2017; Hydock, 2018; Sharpe Wessling et al., 2017). For example, one study found that 89% of participants misrepresented themselves when inclusion criteria were known, while under 5% did so when inclusion criteria were hidden (Sharpe Wessling et al., 2017). Thus, best practices for minimizing disingenuous responding include masking of inclusion criteria. Screening should be conducted as unobtrusively as possible, for example by posting HITs that conceal the population being sampled (e.g., Dunn et al., 2016; Wiens & Walker, 2015) and by utilizing a separate screening questionnaire that masks actual eligibility requirements (Chandler & Shapiro, 2016; Hydock, 2018; Sharpe Wessling et al., 2017; Strickland & Stoops, 2019). Screening questionnaires designed to conceal inclusion criteria often utilize additional questions unrelated to study

eligibility criteria, such as dietary and sleep habits (Boehnke et al., 2021; Dunn et al., 2016; Strickland et al., 2019b; Strickland & Stoops, 2019; Victor et al., 2020). Screening items for the present study are provided in Appendix E.

Inconsistency methods provide another check on data quality post-survey completion. For example, it is recommended to repeat select measures at two separate points during the survey (e.g., screener and main survey) and exclude data from participants who respond inconsistently, minimizing inattentive or disingenuous responding (Chandler & Shapiro, 2016; Strickland & Stoops, 2019). Consistent with prior work (e.g., Strickland & Stoops, 2018; Victor et al., 2020), repeated sets in the present survey included demographic (i.e., marital status) and substance use items (i.e., past-year cigarette use). Data of respondents answering either of the two items inconsistently were excluded.

Improbability methods provided a final check on disingenuous and/or careless responding. Substance use crowdsourcing methodology papers have recommended exclusion of participants who endorse recent use of a number of substances that is considered biologically implausible (e.g., past-year non-medical use of > 35 substances; Black et al., 2019). While co-prescription of 2 or more BZDs is relatively common (e.g., nearly 15% in a pain treatment sample; Mikel et al., 2012; Pandraud-Riguet et al., 2017), participants in the present sample reported up to 8 BZD prescriptions (i.e., selecting every answer choice). The modal number was 1 prescription and median was 2. Based on visual inspection of the distribution and distance from the median, four was considered the maximum number not likely to indicate disingenuous responding, and participants endorsing > 4 BZD prescriptions were excluded from analyses.

Measures

Sociodemographic Characteristics

Participants were asked to report a range of sociodemographic characteristics, including age, racial and ethnic identities, marital status, educational attainment, and household income. Consistent with recent guidance for social sciences and psychology research (Cameron & Stinson, 2019; Hughes et al., 2016; Puckett et al., 2020; Smith et al., 2019), sex was assessed with the item: "What sex were you assigned at birth?" (Female, Male, Intersex), and gender identity was separately assessed. Given previously observed associations with both BZD use (versus non-use; e.g., Cunningham et al., 2017b; Maust et al., 2019; Olfson et al., 2015) and pain (e.g., Fillingim et al., 2009; Mogil, 2012), age and sex were identified as a priori covariates for all analyses.

BZD Prescription

Participants were asked to indicate which type(s) of BZD they were currently prescribed by selecting from among the BZDs assessed in the National Survey on Drug Use and Health, (Substance Abuse and Mental Health Services Administration, 2018), including both generic and brand name examples: alprazolam products (Xanax, Xanax XR, Alprazolam, Extended-Release Alprazolam), lorazepam products (Ativan, Lorazepam), clonazepam products (Klonopin, Clonazepam), diazepam products (Valium, Diazepam), flurazepam (also known as Dalmane), temazepam products (Restoril, Temazepam), triazolam products (Halcion, Triazolam), estazolam products (Prosom), other benzodiazepine tranquilizers or sedatives.

For participants endorsing multiple BZD prescriptions, the primary BZD was defined as that for which the participant's maximum number of past-month days of use was indicated. In other words, primary BZD indicated the participant's most frequently used medication in the past month. Past-month use frequency was calculated as the number of days of use reported by a given participant for his/her primary BZD.

BZD Dependence

The Severity of Dependence Scale (SDS) is a 5-item measure that has been validated as a tool for assessing BZD dependence (Brett & Murnion, 2015; de las Cuevas et al., 2000). Items assess: the extent to which individuals feel their BZD use is out of control, worry about the prospect of missing a dose, worry about their BZD use, wish they could cease BZD use; and how difficult they feel it would be to stop or go without BZDs. Items are rated on a 4-point scale (e.g., 0 'never/almost never' to 4 'always/almost always') and summed to produce a total score (range: 0 to 15), with higher total scores reflecting greater severity of BZD dependence symptoms (i.e., 'dependence severity'). In a sample of 100 individuals reporting BZD use for at least 3 months (de las Cuevas et al., 2000), the mean SDS score was 6.4 (*SD* = 3.8). The SDS has demonstrated diagnostic utility for BZD dependence and use disorders. For example, the SDS has shown sensitivity of 98% and specificity of 94% relative to DSM-IV diagnostic criteria for BZD dependence (using a cutoff score of 6; de las Cuevas et al., 2000) and SDS scores have displayed moderate, positive correlations with DSM-IV criteria for BZD substance dependence (r = 0.65; Cheng et al., 2019). The SDS demonstrated acceptable internal consistency in the present sample (Cronbach's α = .774).

BZD Misuse

Past-12-month BZD misuse was assessed in a manner consistent with current NSDUH definitions, i.e., misuse constitutes a) use without own prescription, b) use in greater amounts, more often, or over a longer period than prescribed, and/or c) use in another way not as directed by a physician (Substance Abuse and Mental Health Services Administration, 2018). Participants were asked to indicate any of the above behaviors that applied to their past-12-month use of BZDs. Consistent with prior literature examining misuse as a binary outcome (e.g., Day &

Rosenthal, 2019; Nicholson & Ford, 2018), participants who endorsered one or more forms of misuse were considered positive for BZD misuse.

BZD Use Frequency

Consistent with previous research, frequency of use was indicated by the self-reported number of days using BZDs over the past month (e.g., Stein et al., 2016). Past-month days of use has reliably been used to index current BZD use frequency (e.g., McHugh et al., 2017; Stein et al., 2016) and identify individuals with current heavier current BZD use for clinical purposes (e.g., informing treatment of concurrent opioid use problems; Stein et al., 2016).

Pain Locations

Participants were asked to mark all locations at which they experienced pain during the past 3 months from among: back, head, face, neck, shoulders, arms, hands, chest, breast, stomach, abdomen, hips, legs, feet, fibromyalgia and/or widespread pain. Participants were then asked to select the primary location from those endorsed.

Chronic Pain Intensity and Pain-Related Disability

The Graded Chronic Pain Scale (GCPS; Von Korff et al., 1992) is a widely used and reliable measure designed to grade the severity of chronic pain, assessing both pain intensity and pain-related disability (Von Korff, 2011). The characteristic pain intensity score ("pain intensity") represents the sum of three NRS items assessing current, past-3-month worst, and past-3-month average pain intensity (0 'no pain' to 10 'pain as bad as it could be'). Higher total scores (range: 0 to 30) represent greater characteristic pain intensity. The pain-related disability score represents the sum of four NRS items assessing the extent to which pain has interfered with daily functioning over the past 3 months (0 'no interference' to 10 'unable to carry on any activities') across 3 domains (daily activities, social/family/recreational, and work) and one item

assessing number of days on which pain interfered with usual activities (0 ‘none’ to 10 = ‘76-90 days’). Higher total scores (range: 0 to 40) represent greater pain-related disability. GCPS pain intensity and pain-related disability subscales demonstrated acceptable and good internal consistency, respectively, in the present sample (Cronbach’s α = .718; α = .859).

Pain Catastrophizing Scale

The Pain Catastrophizing Scale (PCS; Sullivan et al., 1995) is a widely used 13-item measure that has been validated in chronic pain populations (e.g., adult outpatient pain samples; Osman et al., 2000; Sullivan et al., 1995). Respondents are asked the extent to which they experience negative thoughts/emotions in response to pain, rated from 0 (‘not at all’) to 4 (‘all the time’). Items are summed for a total score (range: 0 to 52) with higher total scores reflecting greater tendency to catastrophize when in pain. The PCS is composed of 3 subscales: rumination (e.g., “I keep thinking about how much it hurts”), magnification of pain-related threat (e.g., “I wonder whether something serious might happen”), and feelings of helplessness (e.g., “There’s nothing I can do to reduce the intensity of the pain”). This 3-factor structure has been supported by confirmatory factor analyses (e.g., Osman et al., 2000). The PCS has demonstrated criterion-related validity (i.e., differentiation of community and clinical pain samples); convergent validity via moderate, positive correlations with negative affect and pain intensity and interference (e.g., Osman et al., 2000; Sullivan et al., 1995); and predictive validity in longitudinal studies (e.g., prediction of postoperative pain; Granot & Ferber, 2005; Petersen et al., 2020). In the present sample, the PCS demonstrated excellent internal consistency (Cronbach’s α = .921).

Other Substance Use

Recent epidemiological studies indicate that BZD use is correlated with past-year nicotine use and dependence; alcohol use and use disorders; and prescription opioid use, misuse,

and use disorders (Blanco et al., 2018). Quantity and frequency of alcohol consumption were assessed using the Modified Daily Drinking Questionnaire (DDQ-M; Collins et al., 1985; Dimeff, 1999), which assesses typical weekly drinks per day over the past 3 months, allowing for calculation of weekly averages. Problematic drinking patterns were assessed via the Alcohol Use Disorders Identification Test (AUDIT; Bohn et al., 1995). Reliability and validity of the DDQ-M (Carey et al., 2006) and AUDIT (e.g., Reinert & Allen, 2002) have been demonstrated in previous work. The AUDIT demonstrated excellent internal consistency in the present sample (Cronbach's $\alpha = .908$). Finally, participants were asked to report on use of prescription opioid medications (Substance Abuse and Mental Health Services Administration, 2018) and complete the Current Opioid Use Misuse Measure (COMM; Butler et al., 2007), a measure assessing past-month frequency of aberrant medication-related behaviors (e.g., taking pain medications prescribed to someone else) that has been validated among those prescribed opioids in pain treatment (Butler et al., 2010) and primary care settings (Meltzer et al., 2011).

Other Clinical Characteristics

Generalized anxiety symptoms were measured using the Generalized Anxiety Disorder – 7 item (GAD – 7; Spitzer et al., 2006), a measure with demonstrated reliability and convergent validity in a heterogeneous psychiatric sample (Beard & Björgvinsson, 2014), primary care samples (Spitzer et al., 2006), and the general population (Löwe et al., 2008). The 7 items assessing symptom frequency are rated from 0 ('not at all') to 3 ('nearly every day') and summed for a total score (range: 0 to 21). Scores above 10 are considered to indicate clinically significant anxiety symptoms (Spitzer et al., 2006). The GAD-7 demonstrated good internal consistency (Cronbach's $\alpha = .82$) in the present sample.

The Insomnia Severity Index (ISI; Bastien et al., 2001) is a widely-used 7-item measure of sleep disturbance that has demonstrated reliability and convergent validity in community and clinical samples (e.g., Morin et al., 2011). Items are rated on 5-point Likert-type scales ranging from 0 ('not at all') to 4 ('extremely'), and higher total scores reflect more severe insomnia (range: 0 to 28). Evaluation of two factors, "symptom severity" and "impact on functioning," is supported by results of confirmatory factor analysis (Otte et al., 2019) and differential associations of each factor with relevant clinical correlates (e.g., depressive symptoms; Bazargan et al., 2019). The Severity subscale (i.e., symptom severity) is the sum of 3 items measuring severity of problems with sleep onset, sleep maintenance, and morning awakening, while the Impact subscale (i.e., impact on functioning) is the sum of 3 items measuring distress, interference with daily functioning, and noticeability of impairment. In the present sample, the ISI total, Severity, and Impact scales each demonstrated acceptable internal consistency (Cronbach's $\alpha = .79$, $\alpha = .71$, $\alpha = .70$, respectively).

Data Analytic Plan

All analyses were conducted using SPSS Version 26 (IBM Corp, 2019). First, all variables were assessed for normality (skewness and kurtosis that fall within an acceptable range $-2 \leq x \leq 2$; George & Mallery, 2011). Second, a series of bivariate correlations (continuous variables) and point-biserial correlations (dichotomous variables) were run to test associations between BZD use frequency, BZD dependence, BZD misuse, and participant characteristics (Table 2). Variables that were associated with dependent variables (past-month BZD use frequency, BZD dependence, BZD misuse) were retained as covariates in addition to covariates selected a priori (age, sex; Cunningham et al., 2017b; Maust et al., 2019; Olfson et al., 2015). The variance inflation factor (VIF) for each predictor was also assessed in order to identify

issues of multicollinearity, which can decrease statistical power. Multicollinearity occurs when two or more predictor variables are highly correlated. The VIF is commonly used to quantify a given predictor's inflation of the variance in the regression coefficient, and a VIF ≥ 10 indicates issues with multicollinearity (Myers, 1990).

Each linear regression model was assessed for model assumptions. Linearity of predictor-outcome relationships was indicated by scatterplots of each predictor-outcome pair. Zero mean, equal variance, and independence of residuals were assessed via visual inspection of the residuals versus fitted values plot, and independence of residuals was confirmed via Durbin-Watson statistics falling within the acceptable range ($1 \leq x \leq 3$; Durbin & Watson, 1951). Normality of residuals was assessed using residuals histograms. Models met all assumptions.

The logistic regression model (predicting misuse) was assessed for model assumptions. The dependent variable, misuse, was dichotomous with mutually exclusive and exhaustive categories (yes/no). Linearity of the relationship between predictors and log-odds of the outcome was assessed using the Box-Tidwell procedure (Box & Tidwell, 1962). Linearity assumptions were met for all predictors except pain intensity, for which the Box-Tidwell test suggested a non-linear relationship. However, logistic regression models are considered robust to this violation of linearity at sample sizes above ~250 (e.g., Bergtold et al., 2011).

Next, separate hierarchical linear regression models were conducted to test associations between pain intensity and disability, and BZD dependence severity and past-month use frequency. Covariates were entered in the first step of each model and pain intensity or disability in the second. Relative contributions of pain intensity and disability to observed variance in outcome variables were assessed by examining change in *R*-squared statistic (ΔR^2) at the second

step of each model. A hierarchical logistic regression model was conducted to test associations between pain intensity and disability and likelihood of endorsing any past-year BZD misuse.

We then examined the interaction between pain intensity or disability and pain catastrophizing by including an interaction term (pain intensity or disability x pain catastrophizing) in each model. The order of variables entered in each model were as follows: step 1 (covariates); step 2 (pain intensity or disability, pain catastrophizing); step 3 (pain intensity or disability × pain catastrophizing interaction). In the case of significant interaction terms, we further evaluated interactions using the PROCESS Macro for SPSS (Hayes, 2017) by testing the conditional effects of pain intensity or disability at each of three levels of the moderator (i.e., pain catastrophizing). Consistent with recommendations, associations were probed at the 16th, 50th, and 84th percentiles of PCS Total scores (Hayes, 2017). In the case of non-significant interactions, Step 2 of the model was examined.

Results

Data Quality

Figure 1 summarizes participant flow through screening procedures and reasons for which data were excluded from analysis. A total of 2,379 individuals were screened in Qualtrics, of whom $N = 390$ were eligible and chose to participate. Data were excluded from analysis for any participant who failed inconsistency and/or attention checks ($N = 65$), did not complete measures used as covariates ($N = 8$), or endorsed a number of current BZD prescriptions considered likely to indicate disingenuous or inattentive responding (i.e., ≥ 5 prescriptions; $N = 37$).

Among the remaining $N = 306$ participants included in analyses, there was perfect correspondence between "inconsistency check" items assessed at both the beginning and end of

the survey (i.e., marital status, past-year cigarette use). Correlations in the expected direction were observed between BZD dependence score and hazardous alcohol use patterns (AUDIT total score; $r = .714$) and opioid misuse behaviors (COMM total score; $r = .695$), consistent with previously observed associations of BZD dependence with alcohol/opioid misuse and dependence (e.g., Gudin et al., 2013; Jeffery et al., 2019; McHugh et al., 2020b). As would be expected based on prior literature (e.g., Herrero Babiloni et al., 2020; Lawton & Simpson, 2009; Spitzer et al., 2006), pain intensity was moderately, positively correlated with hazardous alcohol use patterns (AUDIT total score; $r = .482$), generalized anxiety symptoms (GAD - 7 total score; $r = .417$), and insomnia symptoms (ISI total score; $r = .538$).

Participant Characteristics

A total of 390 individuals completed the survey. Following application of data quality checks described above (*Online Survey*), the final sample included 306 adults (38.9% female; $M_{age} = 38.7$, $SD = 11.1$) who reported at least one current BZD prescription. The sample was predominantly white (68.6%) and 2.6% reported Hispanic ethnicity. Over 60% of participants reported earning at least $50,000 in annual household income. Sociodemographic and clinical characteristics are summarized in Table 1.

In terms of pain, participants reported a mean of 77.6 pain days in the past 6 months ($SD = 56.7$). Characteristic pain intensity scores ranged from 5 to 30 ($M = 21.1$, $SD = 4.7$) and pain-related disability scores ranged from 3 to 40 ($M = 25.5$, $SD = 6.9$). Approximately 90% of the sample was classified in GCPS Pain Grades III or IV, indicating moderate to severe pain interference. The most commonly endorsed primary pain locations included back (36.3%) and head/neck (30.7%). Mean PCS score was 30.7 ($SD = 10.5$) indicating high pain catastrophizing on average (Sullivan et al., 1995).

In terms of BZD use, 43.1% of participants reported that first BZD prescription use was longer than 12 months ago. The most commonly reported primary BZDs (i.e., those with highest past-month days of use) were alprazolam (32%), lorazepam (17%), clonazepam (14%), and diazepam (13%). The mean SDS score of 7.7 (*SD* = 3.3) suggests moderate severity of BZD dependence. Mean number of days using BZDs was 14.2 (*SD* = 10.0) in the past month. Participants were asked to indicate all reasons for which a BZD had been prescribed to them, and the most commonly endorsed included anxiety (46%), pain (45%), insomnia (23%), and neurologic conditions (11%). Participants also reported all conditions/symptoms for which they seek relief by taking BZDs, and the most commonly endorsed included pain (56%), anxiety (48%), depression (44%), insomnia/sleep problems (27%), and neurological conditions (11%). For those endorsing multiple conditions/symptoms, the most common combinations were depression-pain (26%), anxiety-depression (23%), anxiety-pain (18%), insomnia-pain (14%), and anxiety-insomnia (13%). Over one-third of the sample reported pain as the main condition/symptom that they seek to relieve by taking BZDs.

Bivariate Correlations

All bivariate correlations are presented in Table 2. Significant associations were observed for past-month days of use with race (white vs. non-white; r = -.185, p = .001) and education (r = -.162, p =.005); for BZD dependence severity with race (r = .165, p = .004) and education (r = .310, p < .001); and for BZD misuse with sex (r = .161, p = .005), race (r = .122, p = .033), and education (r = .334, p = < .001). Therefore, race and education were retained as covariates in all analyses. As expected, pain intensity was highly, positively correlated with pain-related disability (r = .726, p < .001); and moderately, positively correlated with pain catastrophizing (r

= .454, $p < .001$). Further, pain intensity was moderately, positively correlated with BZD dependence severity ($r = .543$, $p < .001$).

Model Assumptions

Models predicting BZD use frequency/dependence severity and likelihood of BZD misuse met assumptions for linear regression and logistic regression, respectively, as described in the Data Analytic Plan. There was no indication of multicollinearity based on VIF for any predictor variable: pain intensity (VIFs < 1.35), pain catastrophizing (VIFs < 1.35), sex (VIFs < 1.05), age (VIFs < 1.15), and education (VIFs < 1.10). Results of hierarchical linear regression and logistic regression models are presented below and in Tables 3-5. Results of pain catastrophizing moderation models can be found in Tables 6-8.

Pain Intensity and Disability and BZD Dependence, Misuse, and Use Frequency

Pain intensity was positively associated with severity of BZD dependence (Table 3; $F[1,299] = 114.863$, $p < .001$, $\Delta R^2 = .245$) and with past-month use frequency (Table 5; $F[1,299] = 5.955$, $p = .015$, $\Delta R^2 = .018$). Pain intensity accounted for 24.5% and 1.8% of unique variance in dependence severity and past-month use frequency, respectively, after accounting for all other variables in the models. Pain-related disability was significantly positively associated with severity of BZD dependence (Table 3; $F[1,299] = 127.156$, $p < .001$, $\Delta R^2 = .264$) and accounted for 26.4% of unique variance in BZD dependence score, after accounting for all other variables in the model. Pain-related disability was not associated with past-month use frequency (Table 5; $F[1,299] = 1.710$, $p = .192$, $\Delta R^2 = .005$).

Greater pain intensity was associated with greater likelihood of endorsing past-year BZD misuse (Table 4; adjusted odds ratio [AOR] = 1.204, 95% confidence interval [CI]: 1.107-1.309, $p < .001$). Specifically, for every one-point increase in pain intensity score, participants were 1.2

times as likely to endorse past-year BZD misuse. Greater pain-related disability was associated with a similar greater likelihood of past-year BZD misuse (Table 4; AOR = 1.147, 95% CI: 1.085-1.212, $p < .001$). Post hoc analyses of misuse subtypes further indicated that pain intensity was positively associated with use without own prescription (AOR = 1.125, 95% CI: 1.057 – 1.197, $p < .001$) and use in greater amounts than prescribed (AOR = 1.078, 95% CI: 1.022 – 1.137, $p = .006$). Pain-related disability was similarly associated with use without own prescription (AOR = 1.102, 95% CI: 1.054-1.152, $p < .001$), use in greater amounts than prescribed (AOR = 1.061, 95% CI: 1.024-1.100, $p = .001$), and use over longer periods of time than prescribed (AOR = 1.042, 95% CI: 1.001-1.084, $p = .043$).

Pain Catastrophizing and BZD Dependence, Misuse, and Use Frequency

In linear regression models assessing *pain intensity x pain catastrophizing* interaction terms (Table 6), pain catastrophizing was positively associated with dependence severity (Step 2; $\beta = .506$, $p < .001$) at Step 2 of the model. In contrast, pain catastrophizing was negatively associated with past-month BZD use frequency (Step 2: $\beta = -.151$, $p = .016$) at Step 2 of the model. Tests examining pain catastrophizing as a moderator of pain intensity-BZD relationships were non-significant (Step 3: ps > .14).

Similarly, in linear regression models assessing *pain-related disability x pain catastrophizing* interaction terms (Table 7), pain catastrophizing was positively associated with BZD dependence severity (Step 2: $\beta = .491$, $p < .001$) at Step 2 of the model. In contrast, pain catastrophizing was not significantly associated with past-month BZD use frequency (Step 2: $\beta = -.128$, $p = .050$) at Step 2 of the model. Tests examining pain catastrophizing as a moderator of pain-related disability-BZD relationships were non-significant (Step 3: ps > .91).

Finally, in logistic regression models assessing *pain intensity or disability x pain catastrophizing* interaction terms (Table 8), pain catastrophizing was positively associated with likelihood of endorsing BZD misuse at Step 2 of both the pain intensity model (Step 2: AOR = 1.122, 95% CI: 1.072-1.174, $p < .001$) and pain-related disability model (Step 2: AOR = 1.115, 95% CI: 1.065-1.168, $p < .001$). Specifically, for every one-point increase in pain catastrophizing score, participants were approximately 1.1 times as likely to endorse past-year BZD misuse after accounting for either pain intensity or pain-related disability. Tests examining pain catastrophizing as a moderator were non-significant (Step 3: *p*s > .09).

Discussion

The current study is the first to examine pain intensity, pain-related disability, and pain catastrophizing in relation to clinically relevant patterns of BZD use (i.e., dependence, misuse) in a chronic pain population. Among a sample of adults with chronic musculoskeletal pain reporting current prescriptions of BZD anxiolytics and/or hypnotics, both chronic pain intensity and disability were positively associated with severity of BZD dependence symptoms and likelihood of BZD misuse, consistent with hypotheses. Pain intensity and pain-related disability accounted for 24.5% and 25.9% of unique variance in BZD dependence, respectively, after controlling for relevant sociodemographic factors. Individuals with greater pain intensity also reported greater past-month days of BZD use, an index of current heaviness of BZD use. Additionally, pain catastrophizing accounted for variance in BZD use outcomes above and beyond that attributable to pain intensity or disability. Notably, over half of all participants endorsed pain as a symptom for which they seek relief by taking BZDs. Overall, these initial findings suggest that individuals with chronic pain who report greater pain intensity or pain-related disability also tend to score higher on indices of clinically relevant BZD use outcomes

(dependence, misuse). Further, results implicate pain catastrophizing in BZD use among individuals with chronic pain.

The present findings of positive covariation of pain intensity and pain-related disability with BZD misuse and dependence build upon a limited literature on pain-BZD relations. Prior studies have found that greater pain intensity is associated with greater likelihood of past-month and current BZD use (Cunningham et al., 2017b; Nielsen et al., 2015), but higher-risk use patterns have been underexamined. Moreover, these findings are largely consistent with an established reciprocal model of pain and substance use (Ditre et al., 2019), which posits that pain and substance use interact in the manner of a positive feedback loop and exacerbate both conditions over time through multiple mechanisms (e.g., dysregulation of overlapping neural reward circuitry; Elman & Borsook, 2016; Simons et al., 2014). Pain is a salient motivator of substance use (e.g., tobacco and alcohol; Ditre & Brandon, 2008; Ditre et al., 2010; Moskal et al., 2018), and substance use in the context of pain may be reinforced via negative affect reduction and pain alleviation (Ditre et al., 2019). Moreover, research on BZD motives specifically has shown that negative affect alleviation and enhancing analgesic effects of other substances (e.g., opioids) are primary motives that individuals report for BZD use (Boyd et al., 2015; Hayashi et al., 2013; McCabe & Cranford, 2012; Vogel et al., 2013). Taken together, this prior literature suggests that pain may be a salient motivator of BZD use. Future experimental and longitudinal research is needed to test whether pain may motivate BZD use and elucidate mechanisms in pain-BZD relations.

Pain catastrophizing scores demonstrated positive associations with BZD dependence but, contrary to expectations, negative associations of small magnitude with past-month days of BZD use. These findings were unexpected given prior research demonstrating positive relations

between pain catastrophizing and likelihood of BZD use (versus non-use) among pain patients (Cunningham et al., 2017b). Several observations may help to explain this discrepancy. First, it is possible that different factors may explain variation in use frequency among a sample all prescribed BZDs, as compared with likelihood of BZD prescription in a sample not selected for BZD use. Second, the present findings are broadly consistent with reports of alcohol use among a chronic pain sample (Nieto et al., 2021). Nieto and colleagues found that pain intensity and pain catastrophizing were both positively associated with alcohol dependence and alcohol craving, while only pain intensity, and not pain catastrophizing, was associated with self-reported alcohol consumption (drinks/day). Thus, pain catastrophizing may be most relevant to outcomes that are closely connected with dependence symptoms (Kneeland et al., 2019; Nieto et al., 2021).

The current results should be interpreted in the context of several limitations. First, these analyses were cross-sectional, thus precluding causal interpretations and inferences regarding directionality. Additional work is needed to elucidate temporal relationships between pain and BZD use, and could draw on methods such as intensive longitudinal designs to examine temporal correspondence between pain experience and BZD self-administration in real-world settings (e.g., Bolger & Laurenceau, 2013). Second, these data were collected via online survey and there was no verification of self-reported medication use, and thus it is possible that participants misrepresented or exaggerated behaviors. Of note, deceptive responding has been shown to decrease in the absence of financial incentives (i.e., when participants cannot tell which responses will allow them access to the study; Sharpe Wessling et al., 2017), and the present study utilized recommended screening methods to conceal inclusion criteria and minimize

financial incentives (see *Method*). Future work may benefit from implementing additional checks (e.g., factual knowledge checking; Chandler & Shapiro, 2016).

Third, it is important to consider issues of generalizability. Mechanical Turk workers have demonstrated demographic differences from nationally representative samples (e.g., higher average educational attainment; Berinsky et al., 2012; Paolacci & Chandler, 2014; Walters et al., 2018), as well as higher prevalence of tobacco cigarette use (22-25%; Johnson et al., 2015; Reese & Veilleux, 2016) and lifetime use of illicit substances (e.g., cocaine, heroin, and methamphetamine; Strickland & Stoops, 2019). Future work is needed to generalize findings across samples recruited via a variety of sampling methods. Finally, given health risks associated with BZD-opioid (e.g., Jeffery et al., 2019; Kandel et al., 2017) and BZD-alcohol co-use (e.g., Jones et al., 2012; Ogbu et al., 2015) and prevalence of both opioid and alcohol use among individuals with chronic pain (e.g., Brennan et al., 2005; Daubresse et al., 2013; Larson et al., 2007), these co-use types are impactful and warrant attention further research among individuals using BZDs in the context of chronic pain.

In summary, this is the first study to examine pain intensity, pain-related disability, and pain catastrophizing in relation to clinically relevant BZD use outcomes, including dependence and misuse, among individuals with chronic pain. The present study builds upon limited prior literature examining BZD use in chronic pain populations, providing initial evidence of positive covariation of several clinically relevant pain characteristics with heavier, more problematic patterns of BZD use. These preliminary findings implicate pain and pain-related cognitive-affective processes in higher-risk BZD use, and suggest that pain relief is a common, yet underrecognized, self-reported motivation for taking BZDs. Limited prior research has examined the role of pain in relation to problematic patterns of BZD use, despite growing concern related

to heavy BZD use, misuse, and dependence in chronic pain populations. Future research should investigate mechanisms in pain-BZD relationships (e.g., negative reinforcement via pain/negative affect reduction, allostatic load processes), as well as contributions of pain to harmful BZD-alcohol and BZD-opioid co-use behaviors.

Table 1

Participant Characteristics

	n (%)
Gender	
Female	119(38.9)
Ethnicity	
Hispanic/Latino	8(2.6)
Race	
American Indian/Alaska Native	8(2.6)
Asian	9(2.9)
Black or African American	75(24.5)
Middle Eastern or North African	2(0.7)
White	210(68.6)
Other	2(0.7)
Marital Status	
Single	38(12.4)
Married	259(84.6)
Divorced/Separated/Widowed	9(2.9)
Education	
High school graduate or GED	7(2.3)
Some college	23(7.5)
Technical/Associates degree	14(4.6)
4-year college degree	174(56.9)
Some school beyond college	11(3.6)
Professional degree (e.g., JD, MD)	77(25.2)
Household Income	
<$10,000	7(2.5)
$10,000-24,999	25(8.2)
$25,000-49,999	89(29.1)
$50,000-$74,999	108(35.3)
≥$75,000	77(25.2)
Anxiety Symptoms [a]	
None to mild	80(26.1)
Moderate to severe	226(73.9)
Hazardous or Harmful Drinking [b]	242(79.1)
Past-6-Month Cannabis Use	136(44.4)
Past-Year Cigarette Use	270(88.2)

	M (SD)	Range
Age	38.7(11.1)	18 - 77
Mean Daily Drinks [c]	1.7(1.9)	0 - 12
Opioid Misuse Behaviors [d]	17.0 (5.6)	0 - 28
ISI [e] total score	16.9(4.8)	1 - 27
ISI Severity score	7.2(2.5)	0 - 12
ISI Impact score	7.5(2.3)	0 - 12

N = 306 unless noted otherwise.
[a] General Anxiety Disorders – 7
[b] Alcohol Use Disorders Identification Test (AUDIT) Score ≥ 8
[c] Modified Daily Drinks Questionnaire (DDQ-M); *N* = 270.
[d] Current Opioid Misuse Measure (COMM); *N* = 268.
[e] Insomnia Severity Index

Table 2

Bivariate and Point-Biserial Correlations Between Sociodemographic, Pain Characteristics, Primary Predictor, and Primary Outcome Variables

Variable	1	2	3	4	5	6	7	8	9	10	11	12
1 Sex	-	-.08	.06	.06	.03	-.10	-.05	.03	.10	-.05	.06	.16**
2 Age		-	-.01	-.05	.02	.26**	.18**	.11	.06	-.04	.01	-.06
3 Race [a]			-	.12*	-.02	.07	.12*	.08	.12*	-.19**	.17**	.12*
4 Education				-	.23**	.01	.16**	.16**	.16**	-.16**	.31**	.33**
5 Income					-	-.17**	.09	.10	-.04	-.10	.06	.01
6 Marital status						-	.06	.11	-.01	-.07	.09	.06
7 Pain intensity [b]							-	.73**	.45**	.08	.54**	.29**
8 Pain-related disability [c]								-	.51**	.03	.57**	.35**
9 Pain catastrophizing [d]									-	-.11	.67**	.45**
10 Past-month use frequency										-	-.05	-.12*
11 Dependence severity [e]											-	.57**
12 Misuse [f]												-

Note. $N = 306$. [a] White versus non-white; [b] Graded Chronic Pain Scale – Characteristic Pain Intensity; [c] Graded Chronic Pain Scale – Disability; [d] Pain Catastrophizing Scale total score; [e] Severity of Dependence Scale total score; [f] No misuse versus any misuse in past year; * $p < .05$; ** $p < .01$.

Table 3
Pain Intensity and Disability on BZD Dependence (Severity of Dependence Scale Score)

	Severity of Dependence Scale Score		
Variable	***β***	***t***	***p***
Sex	.063	1.356	.176
Age	-.064	-1.361	.175
Race	.073	1.554	.121
Education	.212	4.480	< .001**
Pain intensity [a]	.515	10.717	< .001**
R^2		.360	
ΔR^2		.245	
F for ΔR^2		114.863**	
	β	***t***	***p***
Sex	.021	.460	.646
Age	-.030	-.652	.515
Race	.094	2.052	.041*
Education	.210	4.516	< .001**
Pain-Related Disability [b]	.525	11.276	< .001**
R^2		.378	
ΔR^2		.264	
F for ΔR^2		127.156**	

Note: $N = 306$. Results shown are from the second step of each linear regression model; β = standardized beta weights; Sex: Reference group = female; Race: Reference group = white; [a] Graded Chronic Pain Scale – Characteristic Pain Intensity; [b] Graded Chronic Pain Scale – Disability; * $p < .05$, ** $p < .01$

Table 4
Logistic Regression: Pain Intensity and Disability on Likelihood of BZD Misuse

Variable	*B*	*SE*	AOR	95% CI	*p*
Sex	-1.082	.383	.339	.160 - .718	.005**
Age	-.028	.016	.973	.943-.1.004	.083
Race	-.484	.453	.616	.254-1.497	.285
Education	.753	.170	2.123	1.522-2.961	< .001**
Pain intensity [a]	.185	.043	1.204	1.107-1.309	< .001**
Sex	-.920	.385	.399	.188-.848	.017*
Age	-.020	.017	.980	.948-1.013	.224
Race	-.454	.468	.635	.254-1.588	.332
Education	.778	.176	2.178	1.543-3.074	< .001**
Pain-Related Disability [b]	.137	.028	1.147	1.085-1.212	< .001**

Note: $N = 306$. Results shown are from the second step of each logistic regression model; AOR = adjusted odds ratio; Sex: Reference group = female; Race: Reference group = white; [a] Graded Chronic Pain Scale – Characteristic Pain Intensity; [b] Graded Chronic Pain Scale – Disability; * $p < .05$, ** $p < .01$.

Table 5
Pain Intensity and Disability on Past-Month and BZD Use Frequency

	Past-Month Use Frequency		
Variable	***β***	***t***	***p***
Sex	-.031	-.559	.577
Age	-.077	-1.360	.175
Race	-.181	-3.220	.001**
Education	-.165	-2.902	.004**
Pain intensity [a]	.141	2.440	.015*
R^2		.076	
ΔR^2		.018	
F for ΔR^2		5.955*	
	β	***t***	***p***
Sex	-.041	-.725	.469
Age	-.060	-1.059	.291
Race	-.171	-3.028	.003**
Education	-.154	-2.698	.007**
Pain-related disability [b]	.075	1.308	.192
R^2		.063	
ΔR^2		.005	
F for ΔR^2		1.710	

Note: $N = 306$; Results shown are from the second step of each linear regression model; β = standardized beta weights; Sex: Reference group = female; Race: Reference group = white; [a] Graded Chronic Pain Scale—Characteristic Pain Intensity; [b] Graded Chronic Pain Scale—Pain-Related Disability; * $p < .05$, ** $p < .01$.

Table 6

Pain Intensity, Pain Catastrophizing, and BZD Dependence and Use Frequency

BZD Dependence Score					
	β	***t***	***p***	***ΔR²***	***p for ΔR²***
Step 1				.115	< .001**
Sex	.036	.660	.510		
Age	.031	.563	.574		
Race	.128	2.340	.020*		
Education	.294	5.369	< .001**		
Step 2				.442	< .001**
Pain Intensity [a]	.290	6.526	< .001**		
Pain Catastrophizing [b]	.506	11.517	< .001**		
Step 3				.001	.418
Pain Intensity * Pain Catastrophizing	-.181	-.812	.418		
Past-Month BZD Use Frequency					
	β	***t***	***p***	***ΔR²***	***p for ΔR²***
Step 1				.058	.001*
Sex	-.039	-.687	.493		
Age	-.051	-.911	.363		
Race	-.166	-2.946	.003*		
Education	-.142	-2.519	.012*		
Step 2				.036	.003*
Pain Intensity [a]	.208	3.267	.001*		
Pain Catastrophizing [b]	-.151	-2.411	.016*		
Step 3				.007	.142
Pain Intensity * Pain Catastrophizing	-.469	-1.471	.142		

Note: $N = 306$. β = standardized beta weights; Sex: Reference group = female; Race: Reference group = white; [a] Graded Chronic Pain Scale – Characteristic Pain Intensity; [b] Pain Catastrophizing Scale total score; * $p < .05$; ** $p < .001$.

Table 7
Pain-Related Disability, Pain Catastrophizing, and BZD Dependence and Use Frequency

BZD Dependence Score					
	β	***t***	***p***	***ΔR²***	***p for ΔR²***
Step 1				.115	< .001**
Sex	.036	.660	.510		
Age	.031	.563	.574		
Race	.128	2.340	.020*		
Education	.294	5.369	< .001**		
Step 2				.439	< .001**
Pain-Related Disability [a]	.287	6.354	< .001**		
Pain Catastrophizing [b]	.491	10.840	< .001**		
Step 3				.000	.912
Pain-Related Disability * Pain Catastrophizing	-.020	-.111	.912		
Past-Month BZD Use Frequency					
	β	***t***	***p***	***ΔR²***	***p for ΔR²***
Step 1				.058	.001*
Sex	-.039	-.687	.493		
Age	-.051	-.911	.363		
Race	-.166	-2.946	.003*		
Education	-.142	-2.519	.012*		
Step 2				.017	.063
Pain-Related Disability [a]	.137	2.104	.036*		
Pain Catastrophizing [b]	-.128	-1.967	.050		
Step 3				.000	.931
Pain-Related Disability * Pain Catastrophizing	.022	.087	.931		

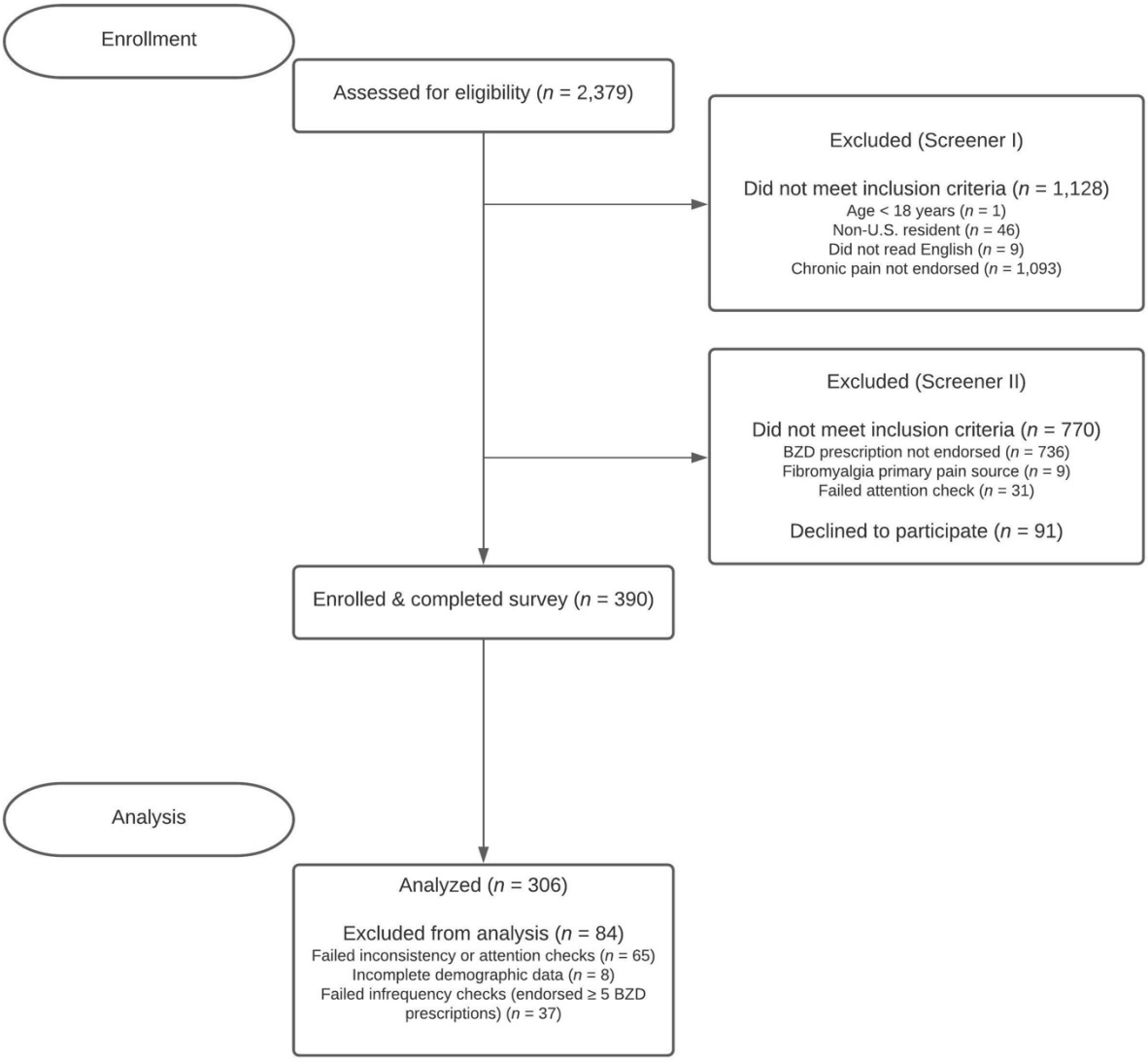
Note: $N = 306$. β = standardized beta weights; Sex: Reference group = female; Race: Reference group = white; [a] Graded Chronic Pain Scale – Disability; [b] Pain Catastrophizing Scale total score; * $p < .05$; ** $p < .001$.

Table 8
Logistic Regression: Pain Intensity and Disability, Pain Catastrophizing, and Likelihood of BZD Misuse

Variable	*B*	*SE*	AOR	95% CI	*p*
Step 1					
Sex	-.871	.356	.418	.208-.841	.015*
Age	-.011	.015	.989	.960-1.019	.454
Race	-.548	.435	.578	.246-1.356	.208
Education	.864	.168	2.373	1.707-3.299	< .001**
Step 2					
Pain Intensity [a]	.107	.054	1.113	1.002-1.237	.046*
Pain Catastrophizing [b]	.115	.023	1.122	1.072-1.174	< .001**
Step 3					
Pain Intensity x Pain Catastrophizing	.008	.005	1.008	.999-1.017	.093
Step 1					
Sex	-.871	.356	.418	.208-.841	.015*
Age	-.011	.015	.989	.960-1.019	.454
Race	-.548	.435	.578	.246-1.356	.208
Education	.864	.168	2.373	1.707-3.299	< .001**
Step 2					
Pain-Related Disability [c]	.078	.033	1.081	1.014-1.153	.017*
Pain Catastrophizing [b]	.109	.023	1.115	1.065-1.168	< .001**
Step 3					
Pain-Related Disability x Pain Catastrophizing	.002	.003	1.002	.996-1.007	.552

Note: $N = 306$. Results shown are from the second step of each logistic regression model; AOR = adjusted odds ratio; Sex: Reference group = female; Race: Reference group = white; [a] Graded Chronic Pain Scale – Characteristic Pain Intensity; [b] Pain Catastrophizing Scale total score; [c] Graded Chronic Pain Scale – Disability; * $p < .05$, ** $p < .01$.

Figure 1. Participant Flow and Data Exclusions



Appendix A

Graded Chronic Pain Scale (GCPS)

1. On how many days in the **last 180 days (6 months)** have you had pain? _____ days

2. How would you rate your pain **RIGHT NOW**?

No Pain										Pain as bad as could be
0	1	2	3	4	5	6	7	8	9	10

3. In the **last 3 months**, how would you rate your WORST pain?

No Pain										Pain as bad as could be
0	1	2	3	4	5	6	7	8	9	10

4. In the **last 3 months**, ON AVERAGE, how would you rate your pain?

No Pain										Pain as bad as could be
0	1	2	3	4	5	6	7	8	9	10

5. In the **last 3 months**, how many days did pain keep you from doing DAILY ACTIVITIES (work, school, homework)?

None	1	2	3-4	5-6	7-19	11-15	16-24	25-60	61-75	76-90

6. In the **last 3 months**, how much has pain interfered with your DAILY ACTIVITIES?

No Interference										Unable to carry on any activities
0	1	2	3	4	5	6	7	8	9	10

7. In the **last 3 months**, how much has pain interfered with your RECREATIONAL, SOCIAL, & FAMILY ACTIVITIES?

No Interference										Unable to carry on any activities
0	1	2	3	4	5	6	7	8	9	10

8. In the **last 3 months**, how much has pain interfered with your ABILITY TO WORK, including housework?

No Interference										Unable to carry on any activities
0	1	2	3	4	5	6	7	8	9	10

Appendix B

Benzodiazepine Types and Benzodiazepine Prescription Assessment

Are you currently prescribed one or more of the following?

- ☐ Alprazolam products (Xanax, Xanax XR, Alprazolam, Extended-Release Alprazolam)
- ☐ Lorazepam products (Ativan, Lorazepam)
- ☐ Clonazepam products (Klonopin, Clonazepam)
- ☐ Diazepam products (Valium, Diazepam)
- ☐ Flurazepam (also known as Dalmane)
- ☐ Temazepam products (Restoril, Temazepam)
- ☐ Triazolam products (Halcion, Triazolam)
- ☐ Estazolam (Prosom)
- ☐ Other benzodiazepine tranquilizers or sedative

Please enter the name of any other benzodiazepine sedative or tranquilizer that is prescribed to you currently. _____

Appendix C

Severity of Dependence Scale (SDS)

Instructions: Consider your use of benzodiazepine sedatives/tranquilizers (such as Xanax/alprazolam, Ativan/lorazepam, Valium/diazepam).

Over the last **3 MONTHS:**

	0 Never/ Almost Never	1 Sometimes	2 Often	3 Always/ Nearly Always
Did you think your use of sedatives/tranquilizers was out of control?				
Did the prospect of missing a dose make you anxious or worried?				
Did you worry about your use of sedatives/tranquilizers?				
Did you wish you could stop?				

How difficult would you find it to stop or go without your sedatives/tranquilizers?

0	1	2	3
Not Difficult	Quite Difficult	Very Difficult	Impossible

Appendix D

Pain Catastrophizing Scale (PCS)

Instructions: We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

When I'm in pain…

	0 Not at all	1 To a slight degree	2 To a moderate degree	3 To a great degree	4 All the time
I worry all the time about whether the pain will end.					
I feel I can't go on.					
It's terrible and I think it's never going to get any better.					
It's awful and I feel that it overwhelms me.					
I feel I can't stand it anymore.					
I become afraid that the pain will get worse.					

I keep thinking of other painful events.	
I anxiously want the pain to go away.	
I can't seem to keep it out of my mind.	
I keep thinking about how much it hurts.	
I keep thinking about how badly I want the pain to stop.	
There's nothing I can do to reduce the intensity of the pain.	
I wonder whether something serious may happen.	

Appendix E

Screening Questions—Part I:

1. What is your age? ____ years

2. What is your country of residence? (*a dropdown menu of all possible responses will be provided*)

3. Do you read English well?

   ___ Yes

   ___ No

4. Have you smoked a cigarette in the past year?

   ___ Yes

   ___ No

5. How many minutes of TV (including movies and online streaming) do you watch per day? (*dropdown of options from 0-1000 minutes, by 10s*)

6. How many minutes of TV (including movies and online streaming) do you think the average person who is your age watches per day? (*dropdown of options from 0-1000 minutes, by 10s*)

7. Would you say that your general health is:

   a. Excellent

b. Very Good

c. Good

d. Fair

e. Poor

f. Don't Know/Not Sure

8. Do you currently suffer from any type of chronic pain, that is, pain that occurs constantly or flares up frequently? Do not report aches and pain that are fleeting or minor.

___ Yes

___ No

9. Are you currently prescribed any of the following medications by your doctor or other healthcare provider?

a. Thyroid medications (such as Levothyroxine)

b. Blood pressure medications (such as Prinivil and Zestril/lisinopril)

c. Cholesterol medications (such as Lipitor/atorvastatin)

d. Diabetes medications (such as metformin)

e. Heartburn medications (such as Prilosec/omeprazole)

f. Antidepressant medications (such as Prozac/fluoxetine, Zoloft/sertraline)

g. Anxiety medications or tranquilizers (Xanax/alprazolam, Ativan/lorazepam, Klonopin/clonazepam, Valium/diazepam, Flexeril, Soma)

h. Sleeping medications (such as Dalmane/flurazepam, Restoril/temazepam, Halcion/triazolam, Lunesta, Ambien)

i. Not Sure/Don't Know

10. What type of soda do you typically drink?

a. Regular

b. Diet

c. Both types

d. I do not drink soda

Screening Questions—Part II

1. Are you currently prescribed one or more of the following?

   __ Alprazolam products (Xanax, Xanax XR, Alprazolam, Extended-Release Alprazolam)

   __ Lorazepam products (Ativan, Lorazepam)

   __ Clonazepam products (Klonopin, Clonazepam)

   __ Diazepam products (Valium, Diazepam)

   __ Cyclobenzaprine (Flexeril)

   __ Soma

   __ Flurazepam (also known as Dalmane)

   __ Temazepam products (Restoril, Temazepam)

   __ Triazolam products (Halcion, Triazolam)

   __ Estazolam (Prosom)

   __ Eszopiclone products (Lunesta)

   __ Zolpidem products (Ambien, Ambien CR, Zolpidem)

   __ Barbiturates (Butisol, Seconal, Phenobarbital)

   __ Other benzodiazepine tranquilizers or sedative

   __ None of the above

   __ Not Sure/Don't Know

   11b. Please enter the name of any other benzodiazepine sedative or tranquilizer that is prescribed to you currently. _____

2. Please **mark all locations** at which you experienced pain during the past 3 months. Then, please **select your primary pain location**, that is, the location that hurts the most.

___ Back
___ Head
___ Face
___ Neck
___ Shoulders
___ Arms
___ Hands
___ Chest
___ Breast
___ Stomach
___ Abdomen
___ Hips
___ Legs
___ Feet
___ Fibromyalgia/widespread pain

3. To monitor quality, please respond with a two for this item.

__ 1
__ 2
__ 3
__ 4
__ 5

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