Current Pain and Headache Reports (2022) 26:575–581
https://doi.org/10.1007/s11916-022-01060-8

ALTERNATIVE TREATMENTS FOR PAIN MEDICINE (M JONES, SECTION EDITOR)

The Impact of Smoking on the Development and Severity of Chronic Pain

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Accepted: 1 May 2022 / Published online: 22 June 2022

Abstract

Purpose of Review The purpose of this review is to examine the impact of smoking and its role on the development of chronic pain and provide a critical review of recent literature.

Recent Findings Recent studies demonstrate the bidirectional and dependent relationship between smoking and chronic pain. Those who are in pain have a more difficult time in the cessation of smoking as well as an increased sensitivity to pain during abstinence, lower confidence, and higher relapse rates. The fear of pain and the anxiety and depression that abstinence causes results in a grim outcome for long-term cessation.

Summary The dependent nature between chronic pain and smoking is affected by numerous variables. Providers should consider a multiprong approach to treating chronic pain and targeting smoking cessation treatment by providing motivational therapy, nicotine replacement, and medication therapies to prevent relapse, and providing those who are more likely to relapse with a higher level of care.

Keywords Chronic pain · Chronic pain development · Smoking · Smoking cessation · Nicotine · Bidirectional relationship

Introduction

The interplay between the development of chronic pain and the use of nicotine-containing products has been hypothesized to affect one another including contributing to the dependence on each other. Nearly 100 million adults in the US population suffer from chronic pain resulting in over $635 billion dollars in lost productivity and medical treatment [1•, 2]. Additionally, smoking remains the leading cause of preventable disease with over 50.6 million American adults endorsing lifetime smoking [3, 4]. Together, smoking and chronic pain amount to almost $1 trillion in lost productivity and medical costs annually [5•, 6].

Though the overall rate of smoking prevalence has declined to 13.7%, this trend has not been seen in chronic pain patients who endorse smoking as rates continue to be elevated (24–68%) [1•, 7•, 8–10]. Chronic pain and nicotine use appear to be interrelated in a positive, bidirectional feedback loop resulting in worsening pain and continued, if not, increased nicotine use with maintenance of both conditions [11, 12•]. Individuals with chronic pain are also twice as likely to smoke [13]. Smokers with anxiety and depression may experience worse pain, pain-induced motivation to smoke, and increased sensitivity to pain during smoking abstinence [14]. Additionally, smoking has been associated with the onset and worsening of chronic pain, and those suffering chronic pain who smoke tend to have higher levels of pain and disability than their nonsmoking counterparts with chronic pain [15–18]. The motivation to smoke can be increased with pain [19–22].

In terms of smoking cessation, those with comorbid chronic pain have a more difficult time quitting than those without chronic pain [23]. Difficulty quitting may stem

This article is part of the Topical Collection on *Alternative Treatments for Pain Medicine*

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from increased sensitivity to pain, or relapse as a result of abstinence-induced pain exacerbation as nicotine has analgesic effects [24•, 25]. The goal of this review is to examine the impact of smoking and its role on the development of chronic pain and provide a critical review of recent literature.

Nicotine as a Risk Factor for the Development of Chronic Pain

Smoking has been implicated as a risk factor in the development of chronic pain conditions such low back pain, lumbar radicular pain, and diabetic peripheral neuropathy [16, 26, 27]. Moreover, the lifetime use of cigarette smoking, as measured by pack-years, has been associated with an increased risk of developing chronic pain [28••]. The mechanisms underlying these associations are not fully understood. A recent study demonstrated the use of pack-years as a predictor of pain reporting with increased pack-years being positively and significantly associated with greater pain severity and frequency of pain [28••]. Additionally, higher pack-years were associated with a higher level of capsaicin-induced intensity, larger areas of mechanical hyperalgesia, and increased pain sensitivity, but was not associated with neurogenic flare, an index of peripheral sensitization [28••]. This study demonstrated evidence for the relation between lifetime smoking exposure and dysregulated pain processing suggesting that central, not peripheral, sensitization may play a role in the development of chronic pain [28••].

Given the results of this study, chronic nicotine use may dysregulate the central mechanisms of pain processing and transmission as nicotinic acetylcholine receptors are found throughout the central regions of pain transmission, spinal dorsal horn, and locus ceruleus [29]. When nicotine induces activation of nicotinic acetylcholine receptors, there is a release of endogenous opioids and norepinephrine which alter central pain processing [28, 29]. Thus, higher pack-years are correlated with increased dysregulation in the central pain processing centers, thereby leading to continued maintenance of both smoking and worsening chronic pain. This study demonstrated the relationship between lifetime smoking and the development of chronic pain as a result of dysregulated central sensitization [28].

The Analgesia and Hyperalgesia of Nicotine

Given that the prevalence of smoking in chronic pain patients is nearly twice that of the general population, one would expect that nicotine would have analgesic effects, yet the effects are shortlived [25, 28••, 30]. A meta-analysis demonstrated that regardless of the delivery of nicotine, it had acute analgesic effects that were small to medium in magnitude [25]. Sex composition was a significant moderator of threshold outcomes with more robust analgesic effects in the studies that had a greater number of men [1•, 25]. This analgesic effect of nicotine may possibly be one of the reasons why quitting in the setting of chronic pain may be quite difficult. In chronic pain patients who smoke, they have reported that smoking was a method to cope with the pain [18, 31]. The analgesic effect of nicotine is believed to act via activation of endogenous opioid, serotonergic, hypothalamic-pituitary-adrenocortical, and sympatho-adrenomedullary systems [29, 32–34]. Additionally, animal models suggest nicotine alters pain sensitivity via altering the expression of glutamate decarboxylase 67, GAD65, μ-opioid receptors, endorphins, and γ-aminobutyric acid which could explain the hyperalgesia and increase in opioid use in smokers in the perioperative period [35•].

Reinforcing the evidence that nicotine has acute analgesic effects, when chronic pain patients who smoked were deprived of nicotine, they exhibited a higher sensitivity to induced pain as compared to nonsmokers and those chronic pain patients who were not deprived of nicotine [24•, 36, 37]. With as short as two hours of nicotine deprivation, users experienced a decrease in pain tolerance indicative of hyperalgesia [36, 37]. Similarly, deprivation resulted in a blunted stress response and an increased pain sensitivity [37]. Even in studies where the majority of patients did not endorse baseline pain, the deprivation of nicotine intake for 12–24 h made this group 3.5 times more likely to endorse pain as compared to the nondeprived group [38•]. Thus, it is likely that this increased pain so early on in smoking cessation may lead individuals to relapse due to hyperalgesia [1•].

The Difficulties with Smoking Cessation in Chronic Pain

Despite the short-term hyperalgesia experienced by individuals who are nicotine deprived, studies have demonstrated that the continued cessation of smoking resulted in improved pain outcomes [39•, 40]. For instance, a reduction in the level of smoking resulted in patients reporting feeling better and having reduced pain [41]. Although the long-term effects of smoking cessation improve overall pain, the ability to quit is hampered by the short-term increase in pain sensitivity as well as the lower confidence in the ability to quit completely [42]. Smokers who reported past-month pain had a lower confidence in remaining abstinent and had greater difficulty in their most recent attempt [42]. Regardless of their lower confidence, smokers in pain reported a greater motivation to quit [42].

Patients have regularly endorsed smoking to cope with the pain of their comorbid disorders and are concerned with the stress that comes with quitting [43]. When compared to

nonsmokers and smokers who did not endorse smoking as a coping strategy, smokers who used smoking to cope scored worse on pain-related outcomes such as an increased pain intensity and the fear of pain [31]. Chronic pain reduces resources such as self-control needed to cope with smoking cessation further increasing the difficulty to maintain abstinence [44]. Patients also expected worsening nicotine withdrawal on future attempts to quit [23]. In addition, smokers in pain identified pain as one of the barriers to cessation of smoking [45]. In a study of 322 smokers, pain severity was significantly and positively related to a perceived barrier to quit [46•]. Furthermore, pain severity predicted a worse negative affect during a smoking cessation [47].

As compared to smokers in pain versus no pain, the withdrawal symptoms were worse in the former [23, 48••]. Persistent pain in smokers predicted a more severe withdrawal, and patients with a higher level of pain-related disability had a shorter latency to relapse [48••]. Moreover, chronic pain patients who smoked experienced worse somatic symptoms during their withdrawal [49].

Other factors such as anxiety and depression, which are quite common in smokers experiencing chronic pain, work in a bidirectional manner leading to worsening pain and the continuation of smoking [5•, 12•, 14]. Evidence points to these comorbidities in smokers leading to functional impairment, motivation to smoke as a result of experienced pain, and increased sensitivity to pain when attempting to be abstinent [11, 14, 20]. Anxiety and depression may present an additional hurdle to the cessation of smoking such that abstinence may lead to increased pain and worsening anxiety and depression, further strengthening this bidirectional relationship [47]. Pain intensity was associated with the desire to smoke and this desire similarly associated with the desire not to relive this negative affect [50•]. This pain-related anxiety has been shown to be a factor in maintaining the dependence on smoking, a barrier to quitting, and the increased levels of smoking [51]. During periods of abstinence, patients had expectations that smoking would improve their overall mood making relapse more likely [52•]. Anxiety sensitivity was positively associated via an increased chronic pain severity with smoking whether it be cigarette or e-cigarette smoking [53•]. Additionally, higher levels of anxiety and pain severity was associated with increased e-cigarette dependence [54].

Predictors of Smoking Cessation

Given that smokers in chronic pain have difficulty with the cessation of pain, being able to predict which patients will have a more difficult time quitting will give providers a better sense for which patients are more likely to need more resources. A recent study used past 2-week pain status as a predictor of achieving cessation milestones such as 7-day point prevalence abstinence, relapse, and 7-day point prevalence abstinence at 2-month follow-up [55••]. They found that smokers with pain versus no pain were less likely to initiate a cessation attempt and achieve 7-day point prevalence abstinence, more likely to relapse, and less likely to achieve a 7-day point prevalence abstinence at 2-month follow-up [55••]. Another study reported results in a cancer cohort and found that those who reported greater pain during the 2-week period were less likely to make an attempt at smoking cessation [56]. In patients with HIV/AIDs, those who reported lower pain intensity over a course of 3 months had a greater likelihood of achieving a 24-h and 7-day point prevalence abstinence [57].

Treatment for Smoking Cessation in the Setting of Chronic Pain

Given that central sensitization may play a role in the development of chronic pain, reducing central sensitization may lower the risk of continued chronic pain and increase the likelihood of smoking cessation. Inhibition with NMDA antagonists has been shown to decrease central sensitization [28••, 58]. In addition to pharmacological interventions to reduce central sensitization, a brief cognitive behavioral intervention reduced central sensitization [59].

Two groups of healthy human subjects were given painful stimuli that led to secondary hyperalgesia with one group receiving a brief pain-focused cognitive training for 5 min which led to a decreased pain unpleasantness but not pain intensity [59]. The secondary hyperalgesia was reduced in the group receiving the pain-focused intervention compared to the group receiving the non-pain-focused intervention [59]. Overall, this study demonstrated that central sensitization can be modified volitionally by altering the pain-related thoughts [59]. Thus, being able to reduce central sensitization by pharmacological and cognitive behavioral methods may mitigate the risk of continued pain after a physical insult or injury and improve outcomes for the cessation of smoking and treating pain [28••, 11, 42].

Additional studies have aimed to target awareness, increase intention to quit, and improve confidence in chronic smokers with comorbid pain. One study looked at HIV patients who were chronic smokers and pain medication users [60•]. Two groups were randomized to receive a computer-based personalized feedback intervention with the other group receiving a control feedback intervention [60•]. The groups receiving the personalized feedback had a greater confidence and intent on quitting, further adding to the evidence that a nonpharmacological, psychoeducation adjunct to treatment of both smoking cessation and chronic pain is needed [41, 60•].

A randomized controlled trial investigated the effects of a brief pain and smoking cessation intervention on individuals with chronic pain since smokers with chronic pain have a greater difficulty with quitting than those without [61••]. Those randomized to the intervention were found to be 7.5 times more likely to endorse a willingness to consider quitting, 2.5 times more likely to report an interest in cessation programs, and 5 times more likely to consider an intensive smoking cessation program [61••]. By promoting awareness and intervening on those with chronic pain who smoke, it can improve the overall trend in the consideration to quit and engage in programs that promote smoking cessation. Further trials and studies continue to support this growing arena of evidence that by providing psychoeducation, intervention, and bringing awareness to smokers with chronic pain, it can tilt the scales towards success for smoking cessation [62••]. Interventions targeting even smokers who were not ready to quit could be considered [62••, 63]. Given this current era of telemedicine and medicine done over electronic means of communications, one study demonstrated that even sessions done over the phone consistently for 8 weeks had resulted in some participants quitting smoking and others reporting improvement in pain intensity [64•]. All these studies taken together demonstrate the effect of awareness and intervening in smokers with chronic pain who may or may not be ready to quit or even consider quitting. Given the social distancing of recent, even simple phone apps to engage smokers not ready to quit may ultimately lead them down the path to either quitting or contemplating quitting [62••].

Discussion

Though these findings detail how interventions can get an individual to want to quit and consider smoking cessation treatment in the short-term, studies are needed to find methods to take this to the next level of long-term smoking cessation. These individuals who are motivated to quit smoking and those who actually engage in smoking cessation treatments should have their treatment tailored to continue to increase their motivation and improve their success for achieving long-term abstinence. Since smokers in chronic pain have increased sensitivity to pain after short-term abstinence, pharmacological methods should be employed to minimize this increased sensitivity [24•]. Studies are needed to better target this intermediate period where the failure rate is so high. Getting over that initial abstinent-increased sensitivity to pain can increase the overall likelihood of maintaining abstinence long-term. By targeting this withdrawal increase in pain with nicotine replacement therapy and/or varenicline, a nicotinic partial agonist, it may lessen the withdrawal and the associated increase in pain sensitivity [65]. Utilizing both nicotine replacement therapy and/or varenicline has been shown to be more effective compared to no treatment in improving smoking abstinence rates; furthermore, these patients with chronic pain are more amenable to trying pharmacological interventions [66, 67].

Overall, it may serve the patient better to target both the chronic pain and the smoking cessation simultaneously all while using interventions to target the motivation to quit. Better collaboration between the pain specialist with the general practitioner may improve the success of both treating the pain and improving the success of long-term abstinence. Furthermore, targeting anxiety and depression that comes along with smoking may provide an additional avenue to further increase the success of smoking cessation long-term. By decreasing the anxiety associated with the fear of pain that comes from abstinence with either therapy or pharmacological methods, individuals may lessen their urge to smoke and have a greater success at smoking cessation. This bidirectional feedback loop can be targeted by using a multidisciplinary approach by targeting (1) the unconscious awareness of the need to quit, (2) improve the motivation to quit, (3) lessen the abstinent increase in pain by using pharmacological methods or psychoeducation, (4) using therapy or medications to target the anxiety and depression associated with smoking, the cessation of smoking, or that which arises during the abstinent period, and (5) using improved communications between providers to ensure proper communications so that all areas are targeted efficiently with appropriate follow-up. Though this may be idealistic, research continues to support approaching chronic pain in the setting of smoking through multiple avenues to achieve the highest success. More research is still needed for patients with chronic pain who smoke to achieve long-lasting abstinence while improving their chronic pain to avoid relapsing during moments of stress or worsening pain.

Additional areas of research are needed regarding other delivery systems of nicotine products such as e-cigarettes as their use has increased even amongst non-tobacco smokers [68, 69•]. Nearly a third of users of e-cigarettes are non-smokers. Are these users also prone to developing chronic pain or is it the additional substances in tobacco smoke that play a role in the development of chronic pain [68]? If this is or is not the case, can these alternative methods of nicotine delivery simultaneously be utilized to wean the chronic smokers and minimize the withdrawal effects on pain. A study demonstrated that the use of e-cigarettes was more effective for the cessation of overall smoking than nicotine replacement therapy implying a behavioral aspect is important for smoking cessation [70••]. By employing numerous methods to target the cessation of smoking, patients can achieve success in cessation all while improving their chronic pain and lessen the burden on their lives.

Compliance with Ethical Standards

Conflict of Interest Christopher Robinson declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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