PERSPECTIVES

Approach to the pharmacological management of chronic pain in patients with an alcohol use disorder

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Abstract: This paper provides an overview of research, guidelines, and clinical considerations for the use of medications for chronic pain in the management of patients with an alcohol use disorder. A review of the literature identified randomized controlled trials, epidemiological cohort studies, consensus guidelines, and one systematic review and meta-analysis. Where gaps in the literature existed, clinical experience of the authors is included. Use of nonopioid medications should be given priority and may offer a more favorable risk profile as well as benefits beyond pain management, such as improvement in anxiety, depression, or insomnia. Pregabalin and gabapentin have additional benefits to decrease alcohol cravings or time to relapse after a period of abstinence from alcohol. Drug interactions between selected analgesics and alcohol, disulfiram, or naltrexone require careful consideration.

Keywords: chronic pain, alcohol use disorder, opioids

Case introduction

A 40-year-old man experienced a work-related accident in 2009 involving his shoulders and wrists. He had a history of alcohol dependence but quit drinking in 1997. At the time of his injury, it was determined that he was at high risk for misuse of opioids. He had no other medical conditions or current medications. After his accident, he resumed drinking to self-manage his pain and continued to drink 12 beers every other day. He was prescribed naltrexone after attending a detoxification program for 1 week, but later discontinued it because of a perceived lack of efficacy. Instead, he planned to cut back slowly and had acknowledged that his pain is a trigger for his drinking.

The patient reported a constant pinching sensation in his right shoulder, into the anterior rotator cuff. He also has pain and numbness in both of his wrists and intermittent numbness on the ulnar aspect of his left hand involving his fourth and fifth fingers. He rated this pain on a visual analog scale as 6/10 most of the time, though it increased to 10/10 quickly with any repetitive use or overhead work.

Rationale

The fictitious case described above is based on the authors' clinical experience with typical patients presenting to healthcare professionals. Chronic pain and alcohol use disorder commonly coexist. One study from Sweden documented a 15.5% prevalence of current or past alcohol dependence among hospitalized chronic pain patients (n=414).[1] Another study from Poland characterized pain in a group of primary alcohol-dependent individuals entering treatment facilities (n=366) and found that 34% of individuals reported moderate or greater physical pain during the previous 4 weeks.[2] Similarly,

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a study from the United States in older adults (n=1,291) identified a higher prevalence of moderate-to-severe pain among problem drinkers (43%) than that observed among nonproblem drinkers (30%).[3] Problematic drinking was defined using the Drinking Problem Index.

Considering potential risks and drug interactions associated with pharmacological management of pain in patients with alcohol use disorders, it is important to use an evidence-informed clinical approach. A review published in 2015 described bidirectional pain–alcohol relations; however, this article did not address management of pain in the presence of problematic alcohol use.[4]

Literature search

Pubmed, Medline, and EMBASE were searched till May 2015 using the terms: acetaminophen, alcohol-related disorders, alcoholic, alcoholism, cannabinoid, chronic pain, duloxetine, ethanol, gabapentin, nabilone, neuralgia, neuropathic pain, opioid, NSAID, pain management, pregabalin, tricyclic antidepressant, and venlafaxine. The search was not restricted by date. Relevant guidelines were also reviewed, including the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain (CNCP)[5] as well as three guidelines on the management of neuropathic pain: the Canadian Pain Society,[6] the International Association for the Study of Pain Neuropathic Pain Special Interest Group,[7] and the European Federation of Neurological Societies.[8] Online drug information databases[9,10] Lexi-Interact™ (Lexi-Comp, Inc., Hudson, OH, USA) and Micromedex® (Thomson Healthcare, Greenwood Village, CO, USA) were searched using the terms acetaminophen, amitriptyline, duloxetine, ethanol, fentanyl, gabapentin, ibuprofen, morphine, nabilone, nabiximols, naproxen, nortriptyline, pregabalin, and venlafaxine for drug interaction information. The approach to the management of a patient with chronic pain in the context of an alcohol use disorder includes clinical experience of the authors and is supported by evidence where referenced.

Diagnosis of underlying cause of chronic pain in a patient with alcohol use disorder

Chronic pain is described as pain lasting longer than 6 months.[5] A biological mechanism should be determined (ie, neuropathic, nociceptive, mixed, or inflammatory). A physical exam and diagnostic tests may be helpful to identify the underlying cause of pain, including: electromyography, nerve conduction studies, X-ray, ultrasound, and/or magnetic resonance imaging depending on physical exam findings.

Peripheral neuropathy related to alcoholism should also be ruled out. The estimated prevalence of alcohol-related neuropathy is 25%–66% among people who meet criteria for alcohol use disorder.[4]

Recommended baseline laboratory tests include alanine aminotransferase (ALT), aspartate aminotransferase, and γ-glutamyl transpeptidase to detect liver injury. Bilirubin and prothrombin time are indicated to assess liver function. Vitamin B$_{12}$, red blood cells, and folate are needed to rule out hematological disorders associated with history of alcohol use disorder. Thyroid-stimulating hormone and fasting blood sugar should be considered for screening, and a clinical assessment of nutritional status is indicated in the context of an alcohol use disorder. The patient should be questioned about their current alcohol consumption. In patients unwilling or unable to provide accurate self-reports, novel alcohol biomarkers may provide helpful screening information and objective evidence of abstinence or relapses.[11,12] The most useful among them are carbohydrate-deficient transferrin (CDT/% CDT), usually measured in serum as the percentage of total transferrin that is carbohydrate deficient, and ethylglucuronide, a direct biomarker as it is an analyte of alcohol metabolism.[11] Ethylglucuronide is a very sensitive indicator of relapse or abstinence as it can be measured at very low concentrations in vivo and returns to normal with 1–3 days of abstinence; however, false positives are possible (eg, from hand sanitizers, mouthwash).[12] CDT is more useful as a screen for heavy alcohol use (5 drinks/day for approximately 2 weeks) and returns to normal after 2–3 weeks of abstinence.[12] It is similar to γ-glutamyl transpeptidase, though more specific.[11] These tests are now widely available in the United States.[12]

A functional assessment (eg, activities of daily living and work) and a psychological screening are highly recommended.

Treatment alternatives for chronic pain in patients with alcohol use disorders

Treatment alternatives for chronic nociceptive pain

Acetaminophen

Chronic alcohol use is an independent risk factor for mortality in acetaminophen toxicity.[13] New recommendations from the United States Food and Drug Administration have reduced the maximum acetaminophen dose for all users from 4 to 3.2 g/day, extra caution remains warranted in heavy drinkers.[5]

Reports have suggested that even therapeutic doses of acetaminophen may be associated with hepatic failure and death in patients with alcohol dependence.[14–16] The time of highest risk for hepatic injury is expected immediately after discontinuation of alcohol intake when the production of N-acetyl-p-benzoquinone imine, the toxic metabolite of acetaminophen, is highest as cytochrome P450 2E1 enzymes remain induced by alcohol for a few days following cassation of chronic exposure.[14] This is also a period when concentrations of glutathione, an antioxidant that converts acetaminophen into a harmless substance, remain depleted in chronic alcohol users. Moreover, concurrent intoxication with alcohol decreases the potential for liver injury by acetaminophen because of competitive inhibition of acetaminophen metabolism by ethanol.[14]

A systematic review and meta-analysis sought to quantify the effect of therapeutic doses of acetaminophen on serum ALT levels in patients who consumed alcohol.[17] This meta-analysis included a total of five randomized, blinded, placebo-controlled trials comparing therapeutic doses of acetaminophen (2–4 g/day, duration of 2–10 days with placebo). Four trials enrolling heavy alcohol users who were admitted to a detoxification center and began acetaminophen within 24 hours of their last drink, one trial enrolled moderate drinkers who continued their normal drinking pattern during the study. The meta-analysis concluded that patients who received acetaminophen in doses up to 4 g/day did not have elevation of their ALT levels on day 4, compared to those who received placebo. The study by Heard et al[18] included in that meta-analysis examined duration of acetaminophen of 10 days and measured ALT on both day 4 and 11 of the study. On day 11, the mean change in ALT was increased in patients receiving acetaminophen over those receiving placebo. This change was not statistically significant, nor were any subjects symptomatic nor meet predefined criteria for hepatotoxicity or liver failure. Similar evidence is not yet available for long-term use of acetaminophen in patients who continue to abuse alcohol.

Nonsteroidal anti-inflammatory drugs

Alcohol consumption can increase risk of nonsteroidal anti-inflammatory drugs (NSAIDs)-related gastrointestinal (GI) effects.[19] Chronic alcohol ingestion together with administration of aspirin may compromise gastroduodenal integrity,[20] and mucosal hemorrhages are often found on endoscopy.[21] Although epidemiology studies examining the association between GI bleed and alcohol consumption have conflicting results, one large case-control study described an increased relative risk of bleeding up to sixfold in current heavy drinkers (≥35 drinks weekly).[22] A small but significant increased risk was also seen in former drinkers.[22] NSAID use and a history of alcohol abuse have resulted in an odds ratio of 10.2 for severe GI events.[23]

In light of the increased risk of GI complications, use of NSAIDs in patients with CNCP and a history or current alcohol use disorder requires caution. If selected, the lowest effective dose is recommended, as NSAID-related GI toxicity is dose dependent.[19,24] For patients who are at high risk of GI bleeding, the addition of a proton-pump inhibitor should be considered.[25] A cyclooxygenase-2 inhibitor may be an appropriate alternative in the absence of cardiovascular risk factors or disease.[24]

Opioids

Before prescribing opioids, screening for the risk of opioid overdose and misuse is necessary (eg, use of the Opioid Risk Tool, which considers the presence of personal or family history of alcohol and substance use, psychiatric conditions, or trauma).[5]

Alcohol is involved in a significant proportion of opioid-related deaths and opioid-abuse-related emergency department visits.[26] When ingested together with certain extended-release (ER) opioid formulations, alcohol disrupts the pharmacokinetic profile and causes "dose dumping" of a toxic amount of opioid in a short period of time.[27,28] One ER hydromorphone formulation was withdrawn from the United States market following concern over the potential for ethanol-induced dose dumping.[28] Pharmacokinetic studies of ER morphine (Kadian® [Actavis Elizabeth LLC, Morristown, NJ, USA]), ER tramadol (Ultram® [Valeant Pharmaceuticals, Laval, QC, Canada], Tridural® [Paladin Labs, Inc., Saint-Laurent, QC, Canada]), and osmotic release oral system (OROS®) hydromorphone (Jurnista™ [Janssen Pharmaceutica NV, Beerse, Belgium]) in the presence of alcohol demonstrated that the kinetics of these products were altered. In the presence of 40% alcohol, Kadian® (Actavis Elizabeth LLC) demonstrated increased C_{max} and decreased t_{max}, though total exposure to drug remained unchanged.[27] After 4 hours of dissolution in the presence of alcohol, the percentage of tramadol released from Ultram® (Valeant Pharmaceuticals) tablets was increased by 40%, whereas conversely the percentage released from Tridural® (Paladin Labs) tablets was decreased in the presence of alcohol. For both preparations, full release of tramadol was observed under all conditions after 24 hours.[29] These effects may be attributed to the differences in the solubilities of the inactive ingredients in alcohol between the controlled-release formulations.[29] Results suggest that Tridural® (Paladin Labs) may be the

preferred tramadol ER formulation for patients who consume it with alcohol, to avoid potential dose dumping. The C_{max} of OROS® (Janssen Pharmaceutica NV) hydromorphone was increased in the presence of alcohol, with a minimal effect on the overall exposure.[30]

A personal history of substance or alcohol abuse is a significant risk factor for opioid misuse.[31,32]

If a trial of opioid therapy is determined to be appropriate despite this risk, current guidelines recommend implementation of structured opioid therapy, including a written opioid agreement that outlines the responsibilities of the physician and the patient, shorter refill frequency, close monitoring, and urine drug screening to discourage aberrant behaviors.[5,19]

Naltrexone, an opioid antagonist, is indicated for the treatment of alcohol dependence as part of a psychotherapeutic program to support abstinence and reduce risk of relapse.[33,34] It does not cause disulfiram-like reactions when alcohol is ingested; however, its opioid antagonistic effects may precipitate acute opioid withdrawal in those who have developed physical dependence from regular opioid use.

Treatment alternatives for chronic neuropathic pain

Three consensus guidelines for the management of neuropathic pain have been published.[6–8] Though selected classes of medications are recommended as first, second, third, or fourth line in the guidelines, evidence is limited and selection of medications depends heavily on individual patient factors. Considerations for use of these medications in a patient with a concurrent alcohol use disorder are presented here.

Tricyclic antidepressants

There are no studies of tricyclic antidepressants (TCAs) for the treatment of co-occurring neuropathic pain and alcohol dependence; however, treatment with TCAs (eg, desipramine, imipramine, amitriptyline) in co-occurring depression and alcohol dependence has been described.[35] All studies demonstrated benefit of the TCA on reducing depressive symptoms; however, two were positive (desipramine, amitriptyline) and one negative (imipramine) for reduction of drinking.[35,36] It has been demonstrated that chronic drinking accelerates clearance of TCAs, likely due to an increased activation of liver enzymes.[35] Higher doses may be required to achieve therapeutic concentrations.[35]

For patients taking disulfiram for management of alcohol use disorder, two case reports have described that use of amitriptyline potentiates the effect of disulfiram and increases the risk of a psychotic and confused mental state.[37] The probable mechanism is elevated levels of various monoamines and potentially increased dopamine levels.[10]

Serotonin–norepinephrine reuptake inhibitors

Ethanol use should be avoided in combination with serotonin–norepinephrine reuptake inhibitors (SNRIs).[38,39] Duloxetine may interact with alcohol to increase the risk of hepatotoxicity or worsen preexisting hepatic disease.[38] The potential for somnolence and the risk of additive central nervous system (CNS) depression are present in select individuals, although small, drug interaction studies have not demonstrated an increase in CNS depression, including psychomotor performance, information processing, and short-term memory, with the combination of SNRIs and alcohol.[40]

Gabapentinoids

Gabapentin and pregabalin have been studied for neuropathic pain, management of alcohol withdrawal, and treatment of relapse. Gabapentin was shown to significantly delay onset to heavy drinking in one small randomized, double blind, placebo-controlled study.[41] Gabapentin in combination with naltrexone has been shown to increase time to relapse and reduce number of drinks per day when compared to naltrexone alone or placebo in another larger, randomized controlled trial.[42] Longer studies are needed to determine if the effect persists. Guglielmo et al[43] conducted a critical review of the literature on pregabalin for alcohol dependence. This review identified five studies, two for alcohol relapse prevention and three for the management of alcohol withdrawal symptoms. For alcohol relapse prevention, there is a randomized, double-blinded study with tiapride and lorazepam as comparators and also a smaller open, prospective study.[43] Pregabalin showed some beneficial effects for reduction of craving, alcohol relapse prevention, and maintenance of abstinence. In the active comparison study, pregabalin was not different from lorazepam but better than tiapride from survival function of time to dropout. For management of alcohol withdrawal symptoms, the review describes one randomized, placebo-controlled trial; one multicenter, randomized single blind trial; and an open label, prospective study. The efficacy of pregabalin for treatment of withdrawal syndrome is still controversial. On the basis of this preliminary evidence, pregabalin or gabapentin are reasonable choices in patients with neuropathic-related pain and co-occurring alcohol dependence who have undergone alcohol detoxification.

For patients who continue to consume alcohol, combination with gabapentinoids has risk of additive CNS depressant effects, including sedation and cognitive impairment.[9]

Cannabinoids

Use of cannabinoids (eg, nabilone, dronabinol, nabiximols) may affect alcohol-related dopamine release, influencing alcohol consumption.[44–46] This may worsen alcohol dependence in the context of concurrent cannabinoid use. Alcohol also causes faster absorption of tetrahydrocannabinol, the key psychoactive ingredient of cannabinoids.[47] Patients who consume both alcohol and cannabinoids may experience increased CNS depressive effects.[48] The combination of alcohol and cannabis can result in dose-related impairments in cognitive and behavioral functions and may adversely affect reaction time and driving ability.[49]

Selected medications used for the treatment of alcohol dependence may interact with cannabinoids. Naltrexone (an opioid antagonist) may increase euphoria from cannabinoids, it seems that this is caused by an interaction at the receptor level.[10,48] There is one case report of a hypomanic episode in a patient with unknown history of bipolar disorder following the use of concomitant disulfiram and cannabinoids.[48]

Given the limited evidence regarding the efficacy of cannabinoids in CNCP, concern about the potential risk of cannabis misuse, and significant psychiatric and neurologic adverse effects, use of cannabinoids for CNCP in the context of alcohol use disorders is generally not recommended.

Conclusion

CNCP is a major problem in society, affecting 25% of the general population.[5] The prevalence of chronic pain is estimated to be higher among patients with substance use disorders than among the general population.[4] The approach to management of CNCP in a patient with a comorbid alcohol use disorder requires careful consideration of risks and benefits of analgesic and adjunctive options for pain, such as acetaminophen, NSAIDs, opioids, antidepressants, anticonvulsants, and cannabinoids. The patient with comorbid alcohol use disorder and chronic pain needs his/her alcohol disorder diagnosed and treated in an integrated way with the treatment of the pain. Considerations about selection of treatment for the pain must depend on treatment strategy and the success of the treatment strategy for the alcohol use disorder.

Acetaminophen may be a reasonable option short-term; however, risks of long-term use of acetaminophen in patients who continue to abuse alcohol remain unquan-

tified.[14,17] Risks associated with NSAID use generally outweigh potential benefits in patients with an alcohol use disorder.[19,20] If NSAID therapy is chosen, the lowest effective dose is recommended and proton-pump inhibitor therapy should be considered in patients at increased risk of GI bleeds.[25] Alcohol increases the risk of overdose and CNS depressant effects of opioids through pharmacokinetic or pharmacodynamic mechanisms.[5,27,28] There is risk of opioid misuse in patients with a history of a substance use disorder.[5] For chronic neuropathic pain, gabapentinoids or SNRIs are alternatives to consider.[6] Pregabalin has demonstrated benefits in preliminary clinical trials for reducing cravings, prolonging time to heavy drinking after withdrawal, and promotion of abstinence.[43] SNRIs and TCAs are first line for treating neuropathic pain; however, their use is limited by adverse effects and drug interactions.[9] Cannabinoids should generally be avoided due to their potential for worsening alcohol dependence and CNS depressant effects.[44–46,48]

Case vignette

The patient's pain was considered to be mixed nature, primarily neuropathic, though there seemed to be some component of nociceptive and, specifically, musculoskeletal pain. Opioids are not a preferred alternative because of the patient's high risk profile for misuse. Because of the patient's reported ongoing use of alcohol, acetaminophen and NSAIDs are not considered safe alternatives. Pregabalin was selected as a preferred therapeutic alternative for the management of the patient's primarily neuropathic pain. It also has potential to decrease cravings for alcohol, which is in line with the patient's goals.

Disclosure

The authors report no conflicts of interest in this work.

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