REVIEW

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Contemporary management of pain in cirrhosis: Toward precision therapy for pain

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Abstract

Chronic pain is highly prevalent in patients with cirrhosis and is associated with poor health-related quality of life and poor functional status. However, there is limited guidance on appropriate pain management in this population, and pharmacologic treatment can be harmful, leading to adverse outcomes, such as gastrointestinal bleeding, renal injury, falls, and hepatic encephalopathy. Chronic pain can be categorized mechanistically into three pain types: nociceptive, neuropathic, and nociplastic, each responsive to different therapies. By discussing the identification, etiology, and treatment of these three mechanistic pain descriptors with a focus on specific challenges in patients with cirrhosis, we provide a framework for better tailoring treatments, including nonpharmacologic therapies, to patients' needs.

INTRODUCTION

Chronic pain in cirrhosis is common, poorly characterized, and uniquely morbid. Reported by 40%–79% of patients with cirrhosis,[1,2] it is a key driver of poor functional status and quality of life.[3–6] Patients with cirrhosis and chronic pain also have significantly greater health care use.[7] Pain management in cirrhosis can be complex because of challenges in diagnosis and medical management. Unfortunately, there is limited guidance outlining optimal pain therapies in this population. Recent guidelines from the American Association for the Study of Liver Disease for palliative care and symptom management in decompensated cirrhosis recommend consulting experts in palliative care, psychiatry, and physical therapy,[8] but pain is common across the spectrum of disease severity, and access to these supportive services can be difficult in many settings. Furthermore, pain phenotypes, each requiring specific treatments, have been poorly characterized in cirrhosis. Thus, proper evaluation and diagnosis are crucial to minimize unnecessary pharmacotherapy and maximize clinical and patient reported outcomes in patients with cirrhosis. Herein, we will define chronic pain mechanistically and discuss the identification, etiology, and treatment options for each type of pain with a focus on unique challenges in patients with cirrhosis.

TYPES OF PAIN

Chronic pain can be characterized using three mechanistic descriptors: nociceptive pain, neuropathic pain,

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and nociplastic pain (Table 1).[9] Nociceptive pain is characterized by ongoing tissue damage or inflammation. Neuropathic pain is characterized by nerve damage in the peripheral or central nervous system (CNS).[9] In contrast, the term "nociplastic pain" was introduced in 2016 to describe pain with no evidence of tissue or nerve damage but with "clinical and psychophysical findings that suggest altered nociception,"[9,10] such as pain associated with fibromyalgia (FM) or irritable bowel syndrome (IBS). [10,11] Patients with nociplastic pain may present with a history of widespread pain refractory to intervention (e.g., opioids, surgery),[12] as well as accompanying CNS-driven complaints (e.g., fatigue, sleep difficulty, mood dysregulation, and memory or concentration problems).[13] The three pain types are not mutually exclusive and can co-occur with variable degrees of overlap.[9]

CHALLENGES IN THE MANAGEMENT OF CHRONIC PAIN

Cirrhosis presents unique challenges in pain management. First, consensus is lacking for the management of pain, and pharmacologic options are limited. There are recommendations to limit the use of acetaminophen (≤ 2 g per day) and avoid nonsteroidal anti-inflammatory drugs (NSAIDs)/opioids.[14,15] If opioids are to be considered, expert opinion recommends weak opioids such as tramadol or hydromorphone for nociceptive pain and tricyclic antidepressants (TCAs) or gabapentin for neuropathic pain.[15] Efficacy data, however, are limited.

Second, virtually any pharmacologic intervention can be difficult and dangerous for patients with cirrhosis.[15] For example, NSAIDs are used by 10%–30% of patients with cirrhosis,[16] increasing the risk of ascites, kidney injury, and gastrointestinal bleeding.[17,18] Even short-term use of NSAIDs can be deleterious, as just five doses of 500 mg of naproxen has been correlated with decreased kidney function, decreased response to furosemide, and inhibited platelet aggregation and thromboxane B_2 production in patients with cirrhosis.[18] Prescription rates for gabapentin have also increased severalfold.[19] Both opioids and gabapentinoids are associated with unique harms in cirrhosis, including worse health-related quality of life (HRQOL)[20] and increased risk of hepatic encephalopathy (HE),[19] a frequent complication of cirrhosis that markedly increases mortality.[21] The mechanisms for the harms of psychoactive medications are multifold. First, cirrhosis pushes toxins from the gastrointestinal tract (e.g., ammonia) that would be normally detoxified by the liver into the bloodstream. These toxins impact brain and muscle function, leading to depression, sleep disturbance, impaired physical function, and poor HRQOL.[3,22]

These toxins lead to a dominant inhibitory tone in the brain that is exacerbated by drugs like gabapentin and benzodiazepines. Second, because opioids prolong intestinal transit time, a key determinant of toxin translocation from the gut, increased toxin load results. Despite the fact that opioids are not thought to be efficacious in chronic noncancer pain[23] and are associated with significant side effects, as many as half of patients with cirrhosis are prescribed opioids.[24,25] Opioid prescription occurs more frequently in cirrhosis than in other chronic diseases[25] and is associated with a higher risk of opioid-related toxicity and overdose in patients with liver disease.[26] Furthermore, opioids are often prescribed with benzodiazepines,[25] compounding the risk of adverse events, including falls[27] and potential overdose deaths.[28] Thus, it is imperative to select pain management modalities to improve pain control while avoiding serious complications (Figure 1). To do so, we need to better understand and characterize the mechanistic drivers of pain in cirrhosis.

OPPORTUNITIES IN THE MANAGEMENT OF CHRONIC PAIN

Pain management is moving toward a precision approach based on the type of pain a patient is experiencing (Figure 2).[9] This is especially true in the setting of central sensitization or nociplastic pain, for which the effective treatments are different than those used to treat nociceptive pain.[9] There are limited data mapping the types of chronic pain that individuals with cirrhosis might experience and to consider the concept of nociplastic pain or "central sensitization" in addition to pain from tissue damage (nociceptive) or nerve damage (neuropathic).[9] Patients with cirrhosis have a disproportionately high burden of nociceptive pain (e.g., fractures, abdominal distension, muscle cramping)[3] and neuropathic pain (e.g., peripheral neuropathy), [29–31] as well as an unknown prevalence of nociplastic pain (e.g., disorders of the brain–gut interaction). However, it is likely that nociplastic pain contributes to the burden of chronic pain in patients with cirrhosis given that multiple common conditions, such as low back pain and osteoarthritis, can be considered "mixed pain" states, in that they can have nociceptive, neuropathic, and/or nociplastic elements.[32] Furthermore, continuous nociceptive pain states (e.g., arthritis, cancer) can lead to nociplastic pain.[9,11]

Optimal treatment for nociplastic pain contrasts with that for nociceptive pain, where therapy is generally peripherally directed (e.g., analgesics, opioids, injections), and instead involves an emphasis on nonpharmacologic therapies.[9] Failure to select therapies for the mechanism of pain will result in suboptimal outcomes. Accordingly, there is a pressing need to

apply tools to identify nociplastic pain in cirrhosis and develop interventions to address it.

A CLOSER LOOK AT NOCIPLASTIC PAIN

In contrast to defining a specific pathology in a given organ, nociplastic pain is an umbrella term that encompasses the variety of conditions characterized by dysfunctional pain processing, such as FM, IBS, temporomandibular disorder, and bladder pain syndrome.[9–11] These conditions are posited to share a common mechanism and therefore tend to overlap within individuals.[11,33]

Mechanisms

The putative cause of nociplastic pain is "central sensitization," characterized by aberrant pain processing in the peripheral and CNS that leads to increased pain sensitivity.[9,11,34] Although various pathways can be disrupted, overall, this aberrancy is defined by augmented pain processing and/or diminished pain inhibition.[9,11] For instance, quantitative sensory testing (QST) techniques can be used to quantify pain sensitivity by applying discrete, measurable stimuli to different areas of the body and observing response (e.g., behavioral responses, pain ratings, and physiological data).[11] QST findings show that temporal summation, designed to evaluate ascending pain

TABLE 1 Mechanistic characterization of pain

	Nociceptive	Neuropathic	Nociplastic
Definition (IASP)[128]	"Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors"[128]	"Pain caused by a lesion or disease of the somatosensory nervous system"[128]	"Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain"[128]
Clinical features	Somatic[113]: Well-localized, reproducible, proportional to injury. Visceral[121]: Diffuse with referred pain, autonomic symptoms (e.g., sweating, nausea, changes in heart rate)	Abnormal sensation with overlying pain in a neuroanatomical distribution[138]	Fluctuating, dull-aching, widespread pain and comorbid symptoms (e.g., sleep, psychological, memory, and/or fatigue problems)[9] ± Sensory sensitivity (e.g., light,[63] smells[64])
Diagnosis/screening	Physical examination, imaging[113]	Physical examination[138,139] ± confirmatory testing[129], screening tools: Neuropathic Pain Questionnaire,[141] painDETECT (PD-Q)[142]	Patient history[9], screening tools: 2016 Fibromyalgia Survey Criteria[9,65]
Treatment	Pharmacologic:[124] NSAIDs, acetaminophen, opioids Interventional:[9,113,123] surgery, injections	Nonpharmacologic:[129,145] adjunct integrative therapies Pharmacologic:[129,139,144] gabapentin/pregabalin, TCA, or SNRI; lidocaine patch, topical capsaicin. Interventional:[129,139] nerve blocks, nerve stimulation, intrathecal therapies	Nonpharmacologic:[9,68] education, self-directed therapies Pharmacologic:[13] Low-dose TCA (e.g., cyclobenzaprine 5–20 mg at bedtime), SNRI (depression, fatigue), gabapentinoids (sleep, anxiety)
Classic examples	Trauma, surgery [114]	Diabetic neuropathy, painful polyneuropathy, painful radiculopathy, trigeminal neuralgia, postherpetic neuralgia, small fiber neuropathy[114,129,130]	Fibromyalgia, irritable bowel syndrome, temporomandibular disorder, bladder pain, pelvic pain[9–11]
Examples in cirrhosis	Fractures,[115] ascites,[116] splenomegaly,[1] muscle cramps,[117] musculoskeletal disease,[118] and mastalgia from aldosterone antagonists[119,120]	Painful peripheral neuropathy[29,31,132–137]	Fibromyalgia[51]

Abbreviations: IASP, International Association for the Study of Pain; NSAID, nonsteroidal anti-inflammatory drug; TCA, tricyclic antidepressant; SNRI, serotonin and norepinephrine reuptake inhibitor.

perception, is enhanced in chronic pain conditions.[35,36] Likewise, conditioned pain modulation, designed to evaluate pain inhibitory pathways, is reduced in those with chronic pain.[37]

Initially, "central sensitization" was thought to reflect spinal amplification of peripheral nociceptive stimuli.[38] However, further research suggested supraspinal involvement, evidenced by QST showing that individuals with chronic pain conditions (e.g., FM, IBS, back pain) have hypersensitivity to pain at the symptomatic site, as well as in asymptomatic body areas.[11,39–41] These findings, along with the common co-occurrence of centrally driven symptoms (i.e., fatigue, sleep difficulty, mood disturbance, and memory problems), indicate that the CNS plays an important role in creating chronic pain states.[9,11,13,42] Furthermore, whereas it was once believed that peripheral nociceptive input was necessary for central sensitization to occur (i.e., a "bottom up" central pain mechanism), central sensitization may also originate within the CNS (i.e., a "top down" central pain mechanism).[11]

Imaging findings exploring brain structure, function, and neurochemistry corroborate and further clarify the role of the CNS in central sensitization.[9,11] Structural MRI studies show differences in gray matter volume for pain processing regions in individuals with chronic pain.[43] Functional MRI data show increased neural connectivity in pain processing regions associated with clinical pain[44] and decreased connectivity following successful pain treatment.[45] In addition, proton MRI spectroscopy shows increased excitatory and decreased inhibitory neurotransmitter levels in pain processing regions associated with chronic pain.[46] Taken together, these results suggest that CNS dysfunction is an important mechanistic driver of pain pathophysiology.[11]

Although chronic pain conditions can involve an interplay of nociceptive, neuropathic, and nociplastic elements,[32] identifying patients who may have higher degrees of nociplastic pain is helpful for treatment purposes, especially in cirrhosis, in which appropriate analgesic use is a complex decision.[15] In general, nonpharmacologic therapies (e.g., exercise, psychological therapies, integrative therapies) are emphasized for the treatment of nociplastic pain,[9,13] as oral analgesics are of limited efficacy in chronic pain, generally,[47] and opioids may make pain in conditions such as FM worse through opioid-induced hyperalgesia.[48] Nociplastic pain conditions are also associated with increased sensitivity to medications and related adverse effects.[49] Furthermore, the comorbid symptoms associated with nociplastic pain provide additional treatment targets.[13,50]

Using what is known about the clinical features, diagnostic methods, and first-line treatments of nociceptive, neuropathic, and nociplastic pain conditions, generally, we can provide a framework for applying these principles to patients with cirrhosis, highlighting considerations specific to liver pathology.

Epidemiology

As a relatively new mechanistic descriptor for chronic pain states,[10] the overall prevalence of nociplastic pain conditions in patients with cirrhosis has not been well documented. A study exploring FM symptoms and liver disease, however, showed that 27% of participants with cirrhosis met criteria for FM: the prototypical nociplastic pain condition.[51] Unsurprisingly, the participants with FM symptoms were also more likely to have mood and
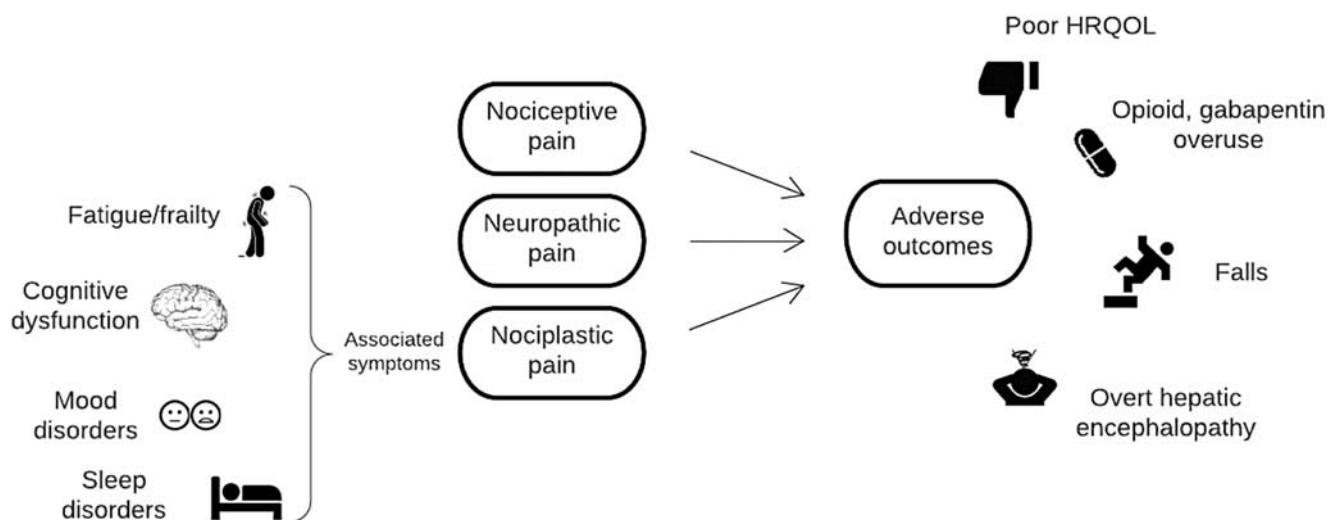

FIGURE 1 Adverse outcomes associated with chronic pain in patients with cirrhosis. Chronic pain, including nociceptive pain, neuropathic pain, and nociplastic pain (along with associated symptoms),[9] is correlated with high rates of opioid[25] and gabapentin[19] prescription in patients with cirrhosis. Both opioid and gabapentinoid use are correlated with poor functional status and quality of life,[3–6] as well as increased risk of hepatic encephalopathy.[19] Furthermore, opioids are often prescribed with benzodiazepines,[25] increasing the risk of falls in patients with cirrhosis.[27] HRQOL, health-related quality of life.
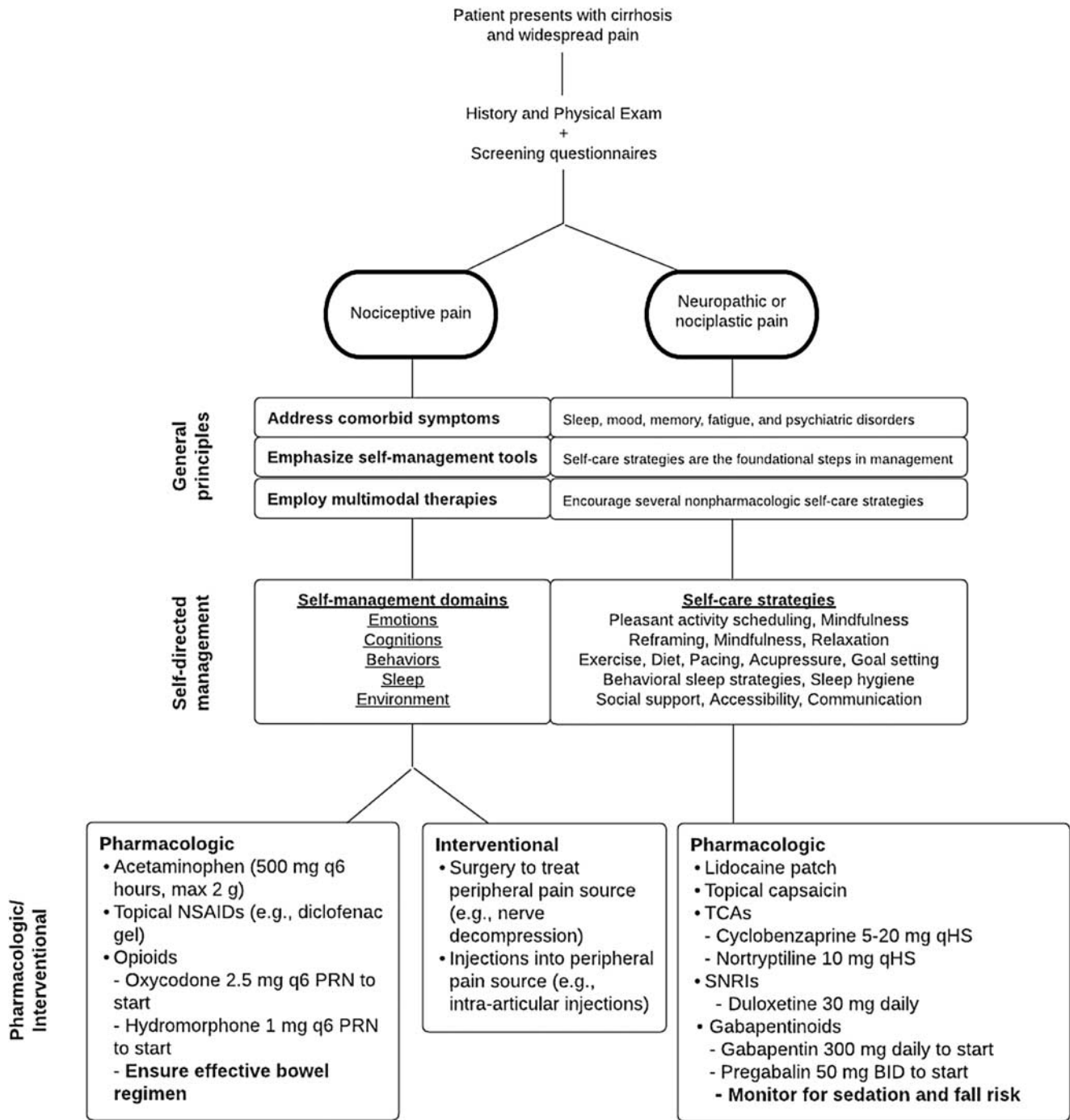
FIGURE 2 Algorithm for the treatment of chronic pain based on mechanism. Summary of recommendations for the evaluation, diagnosis, and treatment of chronic pain in patients with cirrhosis, emphasizing nonpharmacologic therapies as first-line treatment. BID, two times a day; PRN, as needed; q6, every six hours; qHS, every night at bedtime; NSAID, nonsteroidal anti-inflammatory drug; SNRI, serotonin and norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant.

sleep disturbances, reflective of a centralized pain state.[13,51] Despite a lack of research specifically exploring nociplastic pain conditions (i.e., widespread pain, FM, chronic low back pain, temporomandibular disorder, IBS, bladder pain syndrome, pelvic pain)[9] in patients with cirrhosis, there appears to be a correlation between the clinical proxies of central sensitization and cirrhosis.[13] First, sleep quality is generally poor. Among

a cohort of 300 patients with compensated cirrhosis, the prevalence of poor sleep according to the Pittsburgh Index was 63%.[52] Second, depression and anxiety are each prevalent in ≥30% of patients with chronic liver disease, with 18% of patients receiving antidepressants and benzodiazepines.[52,53] Third, fatigue is extremely common but poorly defined.[54] Frailty, defined using physical performance batteries, affects 40%–50% of

patients with cirrhosis.[55–59] Up to 53% of outpatients with compensated cirrhosis cannot perform more than 10 chair stands within 30 seconds.[60] Additionally, 9% of outpatients with compensated cirrhosis are dependent on assistance with activities of daily living,[52] as are 28% of inpatients with cirrhosis without HE and 39% of those with HE.[56] Fourth, cognitive deficits are common, including among patients without prior HE. Cognitive dysfunction in cirrhosis or HE exists as a spectrum from to minimal (subclinical deficits in executive function and motivation) to overt (disorientation and coma). It is estimated that minimal HE is present in up to 60%–80% of patients with cirrhosis.[61] Furthermore, 34% of compensated outpatients have poor executive function skills according to the inhibitory control test.[62] Taken together, these findings indicate that patients with cirrhosis may have a high degree of central sensitization, and thus, nociplastic pain may be an important contributor to chronic pain.

Diagnosis

The diagnosis of nociplastic pain requires provider recognition and characterization including the quality and severity of the pain complaint and associated symptoms, as well as functional status.[9] Classically, patients will report a fluctuating, dull/aching pain that is widespread; however, there may also be a neuropathic element to the pain, described as burning or tingling, for instance.[9,13] Patients may also report associated symptoms (e.g., sleep, psychological, memory, and/or fatigue problems)[9] and/or sensitivity to other sensory stimuli such as light[63] or displeasing smells.[64] Patient history may reveal a long history of pain and/or associated symptoms that were refractory to analgesics or therapies aimed at peripheral pain sites, such as injections.[9] Other indicators of possible nociplastic pain include significant health care use, a high level of distress related to pain, and a family history of chronic pain or psychological disorders.[9] Psychiatric disorders (e.g., mood disorders) are often comorbid with nociplastic pain conditions.[9,11,13] Although there is no established causal link between psychiatric disorders and nociplastic pain, the relationship is likely bidirectional because both conditions have similar risk factors, such as trauma, and related disease mechanisms (i.e., neurotransmitters influencing both pain and mood).[9,11,13] Physical and laboratory examinations are generally unrevealing.[13] Although diagnosis of nociplastic pain is clinical, questionnaires can aid in evaluation of pain location and severity.[9] The 2016 Fibromyalgia Survey Criteria is a self-report tool that assesses pain location (measured by the widespread pain index using a body map) and symptom severity (measured by the symptom severity scale).[9,65] The continuously scaled Fibromyalgia Severity Score can be considered a measure of central sensitization.[9]

Treatment

The approach to nociplastic pain should begin with an accurate diagnosis and empathetic validation from the physician that the patient's symptoms are real.[9] Patient education about nociplastic pain is important, including treatment options and realistic treatment goals, with an emphasis on symptom management, improved quality of life, and maintaining healthy lifestyle habits versus pain elimination.[9] First-line treatment of nociplastic pain should generally start with education and nonpharmacologic self-directed therapies, advancing in a stepwise manner to more intensive interventions as required.[9] This graded approach is endorsed by the US Veterans Health Administration in their "Stepped Care Model of Pain Management."[66,67] In this model, the first step outlines self-care options that can be performed by the patient independently, such as sleep hygiene or relaxation, without the need for an additional provider.[67,68] This step is foundational. A patient engaged in healthy behavioral practices and participating in his/her own pain self-care can help optimize the benefits of professionally led interventions. Step two involves assessment and treatment by a primary care provider and may or may not involve medications.[67] Step three includes secondary consultation, for instance with a therapist for behavioral therapies, such as cognitive behavioral therapy (CBT) or physical therapy.[67] CBT tends to have a small, short-term (1–6 months) benefit in pain and moderate, intermediate-term (6–12 months) benefit in function.[69,70] Step four proposes referral to a tertiary pain center, such as an interventional pain clinic.[67,68]

Beginning with step one, self-management methods not only address pain but can also improve the comorbid symptoms that commonly accompany nociplastic chronic pain, including fatigue, sleep difficulty, mood disturbance, and memory problems.[68] For instance, mindfulness strategies have been shown to improve both depression and sleep quality in men with cirrhosis[71] and have also been shown to improve pain in various chronic pain conditions.[69] Furthermore, improving mood can increase pain tolerance.[68,72]

Self-management strategies can influence the processing of pain via five modalities: mood, cognitions, behaviors, sleep, and environment (Figure 2).[68] Baseline mood and stress levels can impact pain processing.[68,73] Methods like pleasant activity scheduling[74] and mindfulness techniques[75] to improve mood and reduce stress may optimize the conditions under which nociception and, subsequently, pain is experienced by the individual.[68]

Cognitive restructuring can help to change the automatic negative appraisal of pain (e.g., pain catastrophizing) that can influence the context in which pain is experienced. Cognitive restructuring or "reframing" helps to neutralize negative thoughts and emotions that can make pain worse.[68,76,77] Relaxation techniques, such as progressive muscle relaxation or meditation, represent another cognitive approach to decreasing sympathetic nervous system arousal, which can decrease pain and stress.[78] Activities designed to foster emotional resilience, such as savoring positive experiences and practicing gratitude, may improve coping in individuals and provide a background of positivity by which to process the experience of pain.[79]

Behavioral self-management techniques include exercise, diet, and manual therapies (e.g., acupressure and acupuncture).[68] A recent review of exercise for nociplastic pain found that supervised low- to moderate-intensity exercise is helpful in patients with primarily nociplastic pain.[80] Long-term general aerobic, strengthening, or meditative exercises (e.g., tai chi) were recommended.[80] Pacing, whereby individuals schedule activities, breaks, and/or pace activities into shorter tasks, or graded programs, whereby activity is slowly increased, can help improve functioning in those with chronic pain.[81,82]

Although no specific diet is recommended at this time, a recent systematic review of nutritional factors and chronic musculoskeletal pain found support for the pain relieving effects of certain diets in nociplastic conditions, for example vegan and FODMAP diets for FM, a vegetarian diet for general musculoskeletal pain, and caloric restriction for osteoarthritis.[83] Observational research showed that protein intake was positively correlated with pain thresholds in FM, and sugar and fat intake were positively correlated with pain severity in osteoarthritis.[83] Thus, dietary modification may be helpful for certain patients.

Manual therapies, such as acupuncture, have shown efficacy for chronic pain but require a trained practitioner to administer.[84] Acupressure, on the other hand, can be performed by the individual using fingers or objects to put pressure on acupuncture sites.[85] Acupressure has shown efficacy in reducing pain and improving physical function,[85] as well as fatigue.[86]

The association between sleep disruption and chronic pain is well-established, including evidence that this relationship may be bidirectional, with worse pain associated with worse sleep, and vice-versa.[87–91] Traditionally, pain has been thought to lead to sleep disruption[87,92]; however, more recent research has shown that even in healthy individuals, just a single night of sleep deprivation can lead to increased pain sensitivity.[93,94] Thus, methods including behavior change (e.g., sleep schedules, routines) and mind–body exercises (e.g., tai chi, yoga), can be useful.[95]

Social support can positively impact pain experience for those with chronic pain.[96,97] For instance, greater social support has been shown to reduce levels of disability and increase treatment participation.[98] In addition, satisfaction with social support has been linked with greater use and effectiveness of coping strategies.[99] Thus, encouraging meaningful social connection can be a helpful tool.

More recently, various digital self-management tools integrating nonpharmacologic therapies have been developed for chronic pain.[100] Created by our group, www.PainGuide.com is a free, evidence-based digital self-management program for chronic pain grounded in cognitive and behavioral pain management principles focusing on exercise and behavioral interventions for patients with chronic pain.[101–103] An early version of PainGuide (named FibroGuide) was evaluated in a randomized controlled trial with individuals with FM as an unguided, therapist-less intervention. In this study, the digital self-management program demonstrated superior 6-month outcomes for both pain and functional status relative to usual and customary medical care.[104] Other condition-specific versions of PainGuide have demonstrated similar efficacy including for osteoarthritis ("ENGAGE"),[105] chemotherapy-induced peripheral neuropathy ("PROSPECT"),[106] multiple sclerosis (My MSToolkit),[107] and geriatric musculoskeletal pain ("STEPS").[108]

Classic analgesic therapy is of limited efficacy for nociplastic pain,[47] although NSAIDs and acetaminophen may be helpful for relieving peripheral pain that could presumably be contributing to central sensitization.[13] Low-dose tricyclic compounds (e.g., low-dose cyclobenzaprine 5–20 mg at bedtime) are first-line and can relieve multiple symptoms.[13] Otherwise, pharmacologic therapy should generally target symptoms comorbid with pain.[13] For instance, serotonin norepinephrine reuptake inhibitors (SNRIs) (e.g., duloxetine at 30 mg daily) can relieve depression or fatigue, and gabapentinoids can relieve difficulties with sleep or anxiety.[13,109–111] Overall, individualized multimodal therapy should be emphasized.[9]

Despite the risks of analgesic therapies, patients with cirrhosis and their physicians are often afraid to stop opioids and gabapentin.[112] In a qualitative study of semistructured interviews with patients with cirrhosis on opioids and their clinicians, both cited their belief that nonpharmacologic interventions for pain were unproven as the key reason for continuing risky medications.[112] This thinking is erroneous given that no intervention for pain offers more than modest relief for most patients; however, medications tend to have far greater adverse events than do the nonpharmacologic approaches for comparable effect sizes.[13,47] Greater need for education on the merits of nonpharmacologic approaches is needed, as is additional research on implementation of these therapies, including digital self-management programs.

NOCICEPTIVE PAIN

Epidemiology

Nociceptive pain is the most well-understood type of pain, arising from actual or threatened tissue damage.[10] This is pain that occurs as a result of nociceptor activation in a normal sensory nervous system.[10] Although nociceptive pain may play a role in the development of chronic pain,[9,11,113] this type of pain is more likely to be acute, resolving when the injury heals and inflammation decreases.[113,114] In patients with cirrhosis, nociceptive pain can result from diverse causes, including pathologic fractures,[115] ascites,[116] splenomegaly,[1] muscle cramps,[117] musculoskeletal disease (e.g., avascular necrosis, cellulitis, septic arthritis, spondylodiscitis),[118] and mastalgia,[119,120] for instance. Whereas the overall prevalence of nociceptive pain in cirrhosis is not known, the high rate of opioid prescription[24,25] suggests that a substantial proportion of these individuals are at least thought to be experiencing nociceptive pain.

Diagnosis

Generally, somatic nociceptive pain is well-localized, reproducible, and proportional to the injury.[113] Visceral nociceptive pain, conversely, may be diffuse, with referred pain to superficial areas, and can be associated with autonomic symptoms (e.g., sweating, heart rate changes, nausea).[121] Pain descriptors with high specificity for nociceptive pain include heavy, stinging, lacerating, and suffocating.[122] Although diagnosis is not always straightforward, given that pain may be mixed (i.e., with nociceptive, neuropathic, and nociplastic components),[9,32] definitive physical examination or testing (e.g., imaging) can reveal a pain source that is amenable to treatment.[113]

Treatment

The treatment of nociceptive pain generally involves analgesics or interventions directed at the pain source (e.g., surgery to decompress nerves, intra-articular injections).[9,113,123] Common analgesics, such as acetaminophen, NSAIDs (topical and oral), and opioids, are used.[124] Topical NSAIDs treat musculoskeletal injuries with low risk.[124] Oral NSAIDs in patients without portal hypertension, acetaminophen, or both are first-line treatments for mild to moderate pain, based on individual patient risk factors.[124] Muscle relaxants can be used to relieve acute low back and neck pain.[124] Opioids, such as oxycodone or hydrocodone, may be used for acute pain that is severe or unresponsive to initial therapies; however, the recommended usage is for no more than three days given the risks of adverse effects, including complex dependency or even addiction.[124] First-line medications should be continued during this period.[124]

In light of the potential for chronic pain to be mixed,[9,32] as well as for peripheral nociceptive input to lead to central sensitization and nociplastic pain,[9,11] the first-line self-directed nonpharmacologic, noninterventional therapies recommended for nociplastic pain may also be useful in patients who appear to have primarily nociceptive pain. Beginning with these treatments before considering pharmacologic agents or other interventions also aligns with the stepped method recommended for addressing chronic pain, generally.[67,68,125]

Considerations in cirrhosis

NSAIDs are metabolized by the liver and are largely protein-bound, leading to elevated serum levels in patients with cirrhosis.[15] Furthermore, NSAIDs inhibit prostaglandins, leading to decreased renal perfusion and increased risk of hepatorenal syndrome.[15] NSAIDs also inhibit thromboxane A2 production, increasing bleeding risk.[14] Given these risks, oral NSAIDs are contraindicated in cirrhosis.[14,15,126] Topical NSAIDs, such as diclofenac gel, have not been researched in patients with cirrhosis; however, their use is generally accepted because the level of systemic absorption is low.[8] Acetaminophen, although associated with hepatotoxicity when taken in excessive doses, can be used in patients with cirrhosis up to 2 g per day (500 mg every 6 h).[8,14,15,126] Muscle relaxants (e.g., cyclobenzaprine, methocarbamol) are associated with sedation and should be avoided in older individuals[124,127]; however their use in cirrhosis has not been studied. Opioids are primarily metabolized by the liver and are associated with unique risks in cirrhosis, including altered pharmacokinetics (i.e., prolonged half-lives), HE, and risk of addiction in a population with a higher rate of alcoholism.[14,15,126] However, opioids can be started if needed, for instance hydromorphone (1 mg every 6 h as needed) or oxycodone (2.5 mg by mouth every 6–8 h as needed).[8] A fentanyl patch (12 mcg starting dose) can be used in patients without sarcopenia/cachexia or fever.[8]

NEUROPATHIC PAIN

Epidemiology

Neuropathic pain arises from "a lesion or disease of the somatosensory nervous system,"[128] which may result in dysfunctional processing of sensory input in the brain and spinal cord.[129] Neuropathic pain conditions include

diabetic neuropathy, painful polyneuropathy, painful radiculopathy, trigeminal neuralgia, and small fiber neuropathy.[129,130] Peripheral neuropathy, which can be associated with neuropathic pain symptoms,[131] is common in chronic liver disease and appears to be independent of coexisting diabetes or alcohol abuse.[29,31,132–137] Although the prevalence of painful peripheral neuropathy in cirrhosis is unknown, a small study showed that 15% of patients with cirrhosis had symptoms consistent with neuropathy, such as numbness and/or paresthesias.[31]

Diagnosis

The diagnosis of neuropathic pain is typically based on history, physical examination, and potential confirmatory testing.[129] Neuropathic pain is characterized by pain originating from a region of the body with abnormal sensation.[138] Patients may report pain in the absence of any stimulus; pain in response to normally nonpainful stimuli, such as clothing or cold air (allodynia); and/or pain out of proportion to a noxious stimulus (hyperalgesia).[129,138] The character of the pain may range from abnormal sensations (e.g., tingling, numbness), including temperature differences (e.g., burning, cold), to pain that is sharp or stabbing.[129,138,139] The location of pain should follow a neuroanatomical distribution.[138] If a patient presents with neuropathic pain (particularly allodynia in a glove and stocking distribution) and symptoms of dysautonomia (e.g., orthostatic hypotension, dyshidrosis, disorders of micturition, etc.), a diagnosis of small fiber neuropathy should be considered, which is a disease of the small nerve fibers that transmit pain and temperature stimuli.[130,140]

Physical examination will generally reveal sensory examination abnormalities (e.g., to pin prick or thermal testing) in the area of pain.[138,139] Confirmatory testing, including bedside sensory assessment, QST, or neurophysiological techniques (e.g., laser-evoked potentials), can be used for further evaluation.[129] Multiple screening tools have been developed to help identify patients with neuropathic pain, such as the Neuropathic Pain Questionnaire[141] and painDETECT,[142] that include items related to symptoms/signs and may be used as diagnostic aids.[129,143]

Treatment

Treatment of neuropathic pain involves pharmaceuticals and/or local interventions (e.g., nerve blocks).[129] First-line pharmacologic treatment for neuropathic pain is monotherapy with gabapentin or pregabalin, a TCA, or an SNRI.[129,139,144] Lidocaine patches can be used for either isolated symptoms or postherpetic neuralgia.[129,139,144] Topical capsaicin can be used for

peripheral neuropathic pain.[129] If first-line therapies are ineffective or not tolerated, tramadol or oxycodone can be trialed.[129,139,144] Interventional therapies, including nerve blocks, nerve stimulation, and intrathecal therapies, are considered for certain patients if pharmacologic treatment is ineffective or intolerable.[129,139]

Adjunct, noninvasive, nonpharmacologic therapies can also be used.[129,145] A recent review on integrative therapies for painful peripheral neuropathy showed that interventions such as diet and exercise modification, vitamin/antioxidant supplementation, acupuncture, and yoga can be useful for symptom management.[145] Whereas evidence supporting psychological therapies in neuropathic pain is mixed,[146,147] CBT shows a benefit for pain and distress in chronic pain, generally,[70] and thus may be useful in this population, as well.

Considerations in cirrhosis

Lidocaine patches, topical capsaicin, and TCAs are generally appropriate medication options for patients with cirrhosis.[8] SNRIs (e.g, duloxetine, venlafaxine) can be used at low doses, titrated to a maximum of 50% of that used in patients without cirrhosis.[8,109,110] TCAs can be trialed at low doses (e.g., nortriptiline 10 mg nightly); however, the associated sedating and anticholinergic effects can be exacerbated in patients with cirrhosis.[8,15,126] Whereas gabapentin is renally excreted and not hepatically metabolized, it is associated with an increased risk of HE, as well as ataxia and sedation, so should be used with caution and started at low doses (e.g., 300 mg per day).[8,19] Tramadol is felt to have a better adverse effect profile than other opioids, but supportive data are limited in cirrhosis, and it is associated with lowered seizure threshold and risk of serotonin syndrome if combined with medications such as TCAs or selective serotonin reuptake inhibitors.[15,126] Oxycodone has altered pharmacokinetics in cirrhosis but may be started at a low dose (e.g., 2.5 mg by mouth every 6–8 h as needed).[8,126] All opioid medications can cause constipation, increasing the risk of HE.[19]

SUMMARY AND RECOMMENDATIONS

The workup of a patient with cirrhosis and chronic pain should begin with a comprehensive history and physical.[9] The clinical history should evaluate the location, quality, and severity of the pain, as well as functional interference; associated symptoms, including fatigue, sleep difficulty, mood disturbance, and cognitive difficulties; additional sensory sensitivity (e.g., sensitivity to light or sound); and symptoms in other body systems unrelated to the site of pain.[9] In addition to patient history, questionnaires can be useful to evaluate pain location, as well as pain mechanism. For instance,

a body map can be useful to assess pain widespreadedness, with multisite pain indicating a greater likelihood of nociplastic pain.[9,13] The contribution of nociplastic pain can be further assessed using the 2016 Fibromyalgia Survey Criteria.[9,65] The contribution of neuropathic pain can be assessed using the Neuropathic Pain Questionnaire[141] or painDETECT, for example.[142] Physical examination can be useful to identify possible pain generators or sources of nociceptive pain.[9]

In general, the treatment of any type of chronic pain should begin with self-directed nonpharmacologic interventions, as well as the improvement of associated symptoms and treatment of comorbid psychiatric disorders.[9,13,47,66–68,125] The efficacy of any class of analgesic for chronic pain is small to modest, improving symptoms in approximately one of three patients who try them.[47] Opioids are largely ineffective in treating chronic pain,[23] especially nociplastic pain, which can be exacerbated by opioid use.[9,13] Paired with the significant risks of analgesic use in patients with cirrhosis, the risk/benefit ratio is far greater for pharmacologic therapies than nonpharmacologic options in this population; thus, the goal should be to engage patients in actively pursuing these complementary therapies. A recent study to develop a pain self-management intervention for patients with cirrhosis found that participants were highly motivated to pursue nonpharmacologic pain treatments; however, participants cited a lack of simple, evidence-based therapies as a barrier to implementation.[148] In addition to further research on self-management programs, such as PainGuide,[101–103] that can be readily accessed by patients at home, a helpful strategy can be to produce a list of self-directed nonpharmacologic therapies available to treat chronic pain, including exercise, diet modification, and sleep hygiene.[68] The patient should be counseled to choose the interventions they wish to try, with reinforcement from the physician of the import of self-directed management.[68]

Pharmacologic therapy can be used as an adjunct or to address comorbid symptoms in the general population; however, options are very limited in patients with cirrhosis and are associated with adverse effects.[8,13] Topical NSAIDs, such as diclofenac gel, or acetaminophen (500 mg every 6 h, maximum dose of 2 g per day) can be used for nociceptive pain.[8,124] If necessary, opioids can be used in the short term for acute pain (e.g., hydromorphone 1 mg every 6 h as needed; oxycodone 2.5 mg by mouth every 6–8 h as needed; or fentanyl patch in select patients).[8,124] TCAs (e.g., nortriptyline 10 mg nightly) can be used with caution for multiple symptoms, as well as neuropathic pain.[8,13,15,126,129,139,144] Low-dose SNRIs can be used for neuropathic pain or to relieve associated depression or fatigue with a small risk of hepatotoxicity.[8,13,126] Gabapentin at low starting doses (e.g., 300 mg per day) or pregabalin (e.g., 50 mg twice per day) can relieve neuropathic pain or associated sleep difficulties or anxiety.[8,13,129] Lidocaine patches can be used for peripheral neuropathic pain or postherpetic neuralgia.[129,139,144] Topical capsaicin can also be used for peripheral neuropathic pain.[8,129]

CONCLUSION

Chronic pain is highly prevalent in cirrhosis,[1,2] negatively impacting functional status,[3–5] quality of life,[6] and results in increased health care use.[7] Data to guide approaches to chronic pain in cirrhosis are lacking, and pharmacologic intervention is complex with significant potential dangers, namely for opioids and gabapentin, which increase the risk of HE.[19] Chronic pain has multiple phenotypes that are currently not adequately addressed by analgesic therapies. Thus, approaching the treatment of chronic pain with a mechanistic focus is important to improve pain control while maximizing patient safety.

In addition to pain from tissue damage (nociceptive) or nerve damage (neuropathic),[9] nociplastic pain can result from central sensitization, characterized by aberrant pain processing in the peripheral and CNS that leads to increased pain sensitivity,[9,11,34] augmented pain processing, and diminished pain inhibition.[9,11] Patients with cirrhosis experience a high prevalence of nociceptive pain[3] and neuropathic pain,[29–31] but the prevalence of nociplastic pain in this population is understudied. Existing research on FM in cirrhosis,[51] as well as on various symptomatic proxies of central sensitization, such as sleep disturbance,[149] mood dysregulation,[150,151] memory problems,[152] and fatigue,[153] in cirrhosis suggest that nociplastic pain contributes to chronic pain in this population, as well.

Because all pain types can co-occur,[9] interventions to address nociplastic pain may be broadly therapeutic. The treatment of nociplastic pain emphasizes nonpharmacologic management, including self-management techniques addressing mood, cognitions, behaviors, sleep, and environment.[9,68] Future research should continue to explore methods of pain phenotyping, as well as self-management therapies, including implementation tools (e.g., digital programs, app-based programs, etc.). An additional area of future research could involve mechanistic, pharmacologic, and clinical studies to determine the therapeutic windows for currently available pharmacologic therapies for pain in this population, which has been explored for opioids.[154]

AUTHOR CONTRIBUTIONS
Alexis Holman: conceptualization; writing - original draft; writing - review and editing; final review. **Neehar Parikh:** conceptualization; writing - review and editing;

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REFERENCES
1. Rogal SS, Bielefeldt K, Wasan AD, Lotrich FE, Zickmund S, Szigethy E, et al. Inflammation, psychiatric symptoms, and opioid use are associated with pain and disability in patients with cirrhosis. Clin Gastroenterol Hepatol. 2015;13:1009–6.
2. Rakoski MO, McCammon RJ, Piette JD, Iwashyna TJ, Marrero JA, Lok AS, et al. Burden of cirrhosis on older Americans and their families: analysis of the health and retirement study. Hepatology. 2012;55:184–91.
3. Tapper E, Kanwal F, Asrani S, Ho C, Ovchinsky N, Poterucha J, et al. Patient reported outcomes in cirrhosis: a scoping review of the literature. Hepatology (Baltimore, Md.). 2017;67:2375–83.
4. Asrani SK, Ghabril MS, Kuo A, Merriman RB, Morgan T, Parikh ND, et al. Quality measures in HCC care by the Practice Metrics Committee of the American Association for the Study of Liver Diseases. Hepatology. 2021;75:1289–99.
5. Serper M, Parikh ND, Thiele G, Ovchinsky N, Mehta S, Kuo A, et al. Patient-reported outcomes in HCC: a scoping review by the Practice Metrics Committee of the American Association for the Study of Liver Diseases. Hepatology. 2022. https://doi.org/10.1002/hep.32313
6. Gutteling JJ, de Man RA, van der Plas SM, Schalm SW, Busschbach JJ, Darlington AS. Determinants of quality of life in chronic liver patients. Aliment Pharmacol Ther. 2006;23:1629–35.
7. Rogal SS, Winger D, Bielefeldt K, Rollman BL, Szigethy E. Healthcare utilization in chronic liver disease: the importance of pain and prescription opioid use. Liver Int. 2013;33:1497–503.
8. Rogal S, Hansen L, Patel A, Ufere NN, Verma M, Woodrell C, et al. AASLD Practice Guidance: palliative care and symptom-based management in decompensated cirrhosis. Hepatology. 2022.
9. Fitzcharles MA, Cohen SP, Clauw DJ, Littlejohn G, Usui C, Hauser W. Nociplastic pain: towards an understanding of prevalent pain conditions. Lancet. 2021;397:2098–110.
10. Kosek E, Cohen M, Baron R, Gebhart GF, Mico JA, Rice ASC, et al. Do we need a third mechanistic descriptor for chronic pain states? Pain. 2016;157:1382–6.
11. Harte SE, Harris RE, Clauw DJ. The neurobiology of central sensitization. J Appl Biobehav Res. 2018;23:e12137.
12. Brummett CM, Janda AM, Schueller CM, Tsodikov A, Morris M, Williams DA, et al. Survey criteria for fibromyalgia independently predict increased postoperative opioid consumption after lower-extremity joint arthroplasty: a prospective, observational cohort study. Anesthesiology. 2013;119:1434–43.
13. Clauw DJ. Fibromyalgia: a clinical review. JAMA. 2014;311:1547–55.
14. Klinge M, Coppler T, Liebschutz JM, Dugum M, Wassan A, DiMartini A, et al. The assessment and management of pain in cirrhosis. Curr Hepatol Rep. 2018;17:42–51.
15. Chandok N, Watt KD. Pain management in the cirrhotic patient: the clinical challenge. Mayo Clin Proc. 2010;85:451–8.
16. Thomson MJ, Lok AS, Tapper EB. Appropriate and potentially inappropriate medication use in decompensated cirrhosis. Hepatology. 2021;73:2429–40.
17. Lee YC, Chang CH, Lin JW, Chen HC, Lin MS, Lai MS. Non-steroidal anti-inflammatory drugs use and risk of upper gastro-intestinal adverse events in cirrhotic patients. Liver Int. 2012;32:859–66.
18. Clària J, Kent JD, López-Parra M, Escolar G, Ruiz-del-Arbol L, Ginès P, et al. Effects of celecoxib and naproxen on renal function in nonazotemic patients with cirrhosis and ascites. Hepatology. 2005;41:579–87.
19. Tapper EB, Henderson JB, Parikh ND, Ioannou GN, Lok AS. Incidence of and risk factors for hepatic encephalopathy in a population-based cohort of Americans with cirrhosis. Hepatol Commun. 2019;3:1510–9.
20. Tapper EB, Baki J, Parikh ND, Lok AS. Frailty, psychoactive medications, and cognitive dysfunction are associated with poor patient-reported outcomes in cirrhosis. Hepatology. 2019;69:1676–85.
21. Jepsen P, Ott P, Andersen PK, Sorensen HT, Vilstrup H. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. Hepatology. 2010;51:1675–82.
22. Kronsten VT, Tranah TH, Pariante C, Shawcross DL. Gut-derived systemic inflammation as a driver of depression in chronic liver disease. J Hepatol. 2021;76:665–80.
23. Reinecke H, Weber C, Lange K, Simon M, Stein C, Sorgatz H. Analgesic efficacy of opioids in chronic pain: recent meta-analyses. Br J Pharmacol. 2015;172:324–33.
24. Rogal SS, Beste LA, Youk A, Fine MJ, Ketterer B, Zhang H, et al. Characteristics of opioid prescriptions to veterans with cirrhosis. Clin Gastroenterol Hepatol. 2018;17:1165–4.e3.
25. Konerman MA, Rogers M, Kenney B, Singal AG, Tapper E, Sharma P, et al. Opioid and benzodiazepine prescription among patients with cirrhosis compared to other forms of chronic disease. BMJ Open Gastroenterol. 2019;6:e000271.
26. Zedler B, Xie L, Wang L, Joyce A, Vick C, Kariburyo F, et al. Risk factors for serious prescription opioid-related toxicity or overdose among Veterans Health Administration patients. Pain Med. 2014;15:1911–29.
27. Tapper EB, Risech-Neyman Y, Sengupta N. Psychoactive medications increase the risk of falls and fall-related injuries in hospitalized patients with cirrhosis. Clin Gastroenterol Hepatol. 2015;13:1670–5.
28. Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, Mackey S. Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis. BMJ. 2017;356:j760.
29. McDougall AJ, Davies L, McCaughan GW. Autonomic and peripheral neuropathy in endstage liver disease and following liver transplantation. Muscle Nerve. 2003;28:595–600.
30. Williams KH, Burns K, Constantino M, Shackel NA, Prakoso E, Wong J, et al. An association of large-fibre peripheral nerve dysfunction with non-invasive measures of liver fibrosis secondary to non-alcoholic fatty liver disease in diabetes. J Diabetes Complications. 2015;29:1240–7.

31. Kharbanda PS, Prabhakar S, Chawla YK, Das CP, Syal P. Peripheral neuropathy in liver cirrhosis. J Gastroenterol Hepatol. 2003;18:922–6.

32. Freynhagen R, Parada HA, Calderon-Ospina CA, Chen J, Rakhmawati Emril D, Fernandez-Villacorta FJ, et al. Current understanding of the mixed pain concept: a brief narrative review. Curr Med Res Opin. 2019;35:1011–8.

33. Maixner W, Fillingim RB, Williams DA, Smith SB, Slade GD. Overlapping chronic pain conditions: implications for diagnosis and classification. J Pain. 2016;17:T93–107.

34. Woolf CJ. Central sensitization: implications for the diagnosis and treatment of pain. Pain. 2011;152:S2–15.

35. Staud R, Cannon RC, Mauderli AP, Robinson ME, Price DD, Vierck CJ Jr. Temporal summation of pain from mechanical stimulation of muscle tissue in normal controls and subjects with fibromyalgia syndrome. Pain. 2003;102:87–95.

36. Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, Simonsen OH, et al. Sensitization in patients with painful knee osteoarthritis. Pain. 2010;149:573–81.

37. Lewis GN, Rice DA, McNair PJ. Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis. J Pain. 2012;13:936–44.

38. Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states. Pain. 1991;44:293–9.

39. Gibson SJ, Littlejohn GO, Gorman MM, Helme RD, Granges G. Altered heat pain thresholds and cerebral event-related potentials following painful CO_2 laser stimulation in subjects with fibromyalgia syndrome. Pain. 1994;58:185–93.

40. Wilder-Smith CH, Robert-Yap J. Abnormal endogenous pain modulation and somatic and visceral hypersensitivity in female patients with irritable bowel syndrome. World J Gastroenterol. 2007;13:3699–704.

41. Leffler AS, Hansson P, Kosek E. Somatosensory perception in a remote pain-free area and function of diffuse noxious inhibitory controls (DNIC) in patients suffering from long-term trapezius myalgia. Eur J Pain. 2002;6:149–59.

42. Phillips K, Clauw DJ. Central pain mechanisms in the rheumatic diseases: future directions. Arthritis Rheum. 2013;65:291–302.

43. Smallwood RF, Laird AR, Ramage AE, Parkinson AL, Lewis J, Clauw DJ, et al. Structural brain anomalies and chronic pain: a quantitative meta-analysis of gray matter volume. J Pain. 2013;14:663–75.

44. Napadow V, LaCount L, Park K, As-Sanie S, Clauw DJ, Harris RE. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. Arthritis Rheum. 2010;62:2545–55.

45. Napadow V, Kim J, Clauw DJ, Harris RE. Decreased intrinsic brain connectivity is associated with reduced clinical pain in fibromyalgia. Arthritis Rheum. 2012;64:2398–403.

46. Harris RE, Clauw DJ. Imaging central neurochemical alterations in chronic pain with proton magnetic resonance spectroscopy. Neurosci Lett. 2012;520:192–6.

47. Clauw DJ. Pain management: fibromyalgia drugs are 'as good as it gets' in chronic pain. Nat Rev Rheumatol. 2010;6:439–0.

48. Jackson D, Singh S, Zhang-James Y, Faraone S, Johnson B. The effects of low dose naltrexone on opioid induced hyper-algesia and fibromyalgia. Front Psych. 2021;12:593842.

49. Jason LA, Taylor RR, Kennedy CL. Chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities in a community-based sample of persons with chronic fatigue syndrome-like symptoms. Psychosom Med. 2000;62:655–3.

50. Williams DA. Phenotypic features of central sensitization. J Appl Biobehav Res. 2018;23:e12135.

51. Rogal SS, Bielefeldt K, Wasan AD, Szigethy E, Lotrich F, DiMartini AF. Fibromyalgia symptoms and cirrhosis. Dig Dis Sci. 2015;60:1482–9.

52. Tapper EB, Baki J, Parikh ND, Lok AS. Frailty, psychoactive medications, and cognitive dysfunction are associated with poor patient-reported outcomes in cirrhosis. Hepatology. 2018.

53. Balp MM, Krieger N, Przybysz R, Way N, Cai J, Zappe D, et al. The burden of nonalcoholic steatohepatitis (NASH) among patients from Europe: a real-world patient-reported outcomes study. JHEP Rep. 2019;1:154–61.

54. Swain MG, Jones DE. Fatigue in chronic liver disease: new insights and therapeutic approaches. Liver Int. 2019;39:6–19.

55. Tapper EB, Konerman M, Murphy S, Sonnenday CJ. Hepatic encephalopathy impacts the predictive value of the Fried Frailty Index. Am J Transplant. 2018;18:2566–70.

56. Tapper EB, Finkelstein D, Mittleman MA, Piatkowski G, Lai M. Standard assessments of frailty are validated predictors of mortality in hospitalized patients with cirrhosis. Hepatology. 2015;62:584–90.

57. Lai JC, Sonnenday CJ, Tapper EB, Duarte-Rojo A, Dunn MA, Bernal W, et al. Frailty in liver transplantation: an expert opinion statement from the American Society of Transplantation Liver and Intestinal Community of Practice. Am J Transplant. 2019;19:1896–906.

58. Lai JC, Feng S, Terrault NA, Lizaola B, Hayssen H, Covinsky K. Frailty predicts waitlist mortality in liver transplant candidates. Am J Transplant. 2014;14:1870–9.

59. Lai JC, Covinsky KE, Dodge JL, Boscardin WJ, Segev DL, Roberts JP, et al. Development of a novel frailty index to predict mortality in patients with end-stage liver disease. Hepatology. 2017;66:564–74.

60. Tapper EB, Derstine B, Baki J, Su GL. Bedside measures of frailty and cognitive function correlate with sarcopenia in patients with cirrhosis. Dig Dis Sci. 2019;64(12):3652–9.

61. Tapper EB, Parikh ND, Waljee AK, Volk M, Carlozzi NE, Lok AS. Diagnosis of minimal hepatic encephalopathy: a systematic review of point-of-care diagnostic tests. Am J Gastroenterol. 2018;113:529–38.

62. Tapper EB, Zhao L, Nikirk S, Baki J, Parikh ND, Lok AS, et al. Incidence and bedside predictors of the first episode of overt hepatic encephalopathy in patients with cirrhosis. Am J Gastroenterol. 2020;115:2017–25.

63. Martenson ME, Halawa OI, Tonsfeldt KJ, Maxwell CA, Hammack N, Mist SD, et al. A possible neural mechanism for photosensitivity in chronic pain. Pain. 2016;157:868–78.

64. Schweinhardt P, Sauro KM, Bushnell MC. Fibromyalgia: a disorder of the brain? Neuroscientist. 2008;14:415–21.

65. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Häuser W, Katz RL, et al. 2016 Revisions to the 2010/2011 fibromyalgia diagnostic criteria. Semin Arthritis Rheum. 2016;46:319–29.

66. Kerns RD, Philip EJ, Lee AW, Rosenberger PH. Implementation of the veterans health administration national pain management strategy. Transl Behav Med. 2011;1:635–43.

67. Cosio D, Schafer T. Implementing an acceptance and commit-ment therapy group protocol with veterans using VA's stepped care model of pain management. J Behav Med. 2015;38:984–97.

68. Williams DA, Cooper S. Patient education and self-managment. In: Benzon HRJ, Wu CL, et al, editors. Practical management of pain. 6th ed. New York, NY: Elsevier; 2023.

69. Skelly AC, Chou R, Dettori JR, Turner JA, Friedly JL, Rundell SD, et al. Noninvasive nonpharmacological treatment for chronic pain: a systematic review update. Rockville, MD: Agency for Healthcare Research and Quality; 2020.

70. Williams ACC, Fisher E, Hearn L, Eccleston C. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev. 2020;8:CD007407.

71. Bajaj JS, Ellwood M, Ainger T, Burroughs T, Fagan A, Gavis EA, et al. Mindfulness-based stress reduction therapy improves patient and caregiver-reported outcomes in cirrhosis. Clin Transl Gastroenterol. 2017;8:e108.

72. Tang NKY, Salkovskis PM, Hodges A, Wright KJ, Hanna M, Hester J. Effects of mood on pain responses and pain tolerance: an experimental study in chronic back pain patients. Pain. 2008;138:392–401.

73. Davis MC, Thummala K, Zautra AJ. Stress-related clinical pain and mood in women with chronic pain: moderating effects of depression and positive mood induction. Ann Behav Med. 2014;48:61–70.

74. Riebe G, Fan MY, Unutzer J, Vannoy S. Activity scheduling as a core component of effective care management for late-life depression. Int J Geriatr Psychiatry. 2012;27:1298–304.

75. Cherkin DC, Sherman KJ, Balderson BH, Cook AJ, Anderson ML, Hawkes RJ, et al. Effect of mindfulness-based stress reduction vs cognitive behavioral therapy or usual care on back pain and functional limitations in adults with chronic low back pain: a randomized clinical trial. JAMA. 2016;315:1240–9.

76. Martinez-Calderon J, Jensen MP, Morales-Asencio JM, Luque-Suarez A. Pain catastrophizing and function in individuals with chronic musculoskeletal pain: a systematic review and meta-analysis. Clin J Pain. 2019;35:279–93.

77. Smeets RJ, Vlaeyen JW, Kester AD, Knottnerus JA. Reduction of pain catastrophizing mediates the outcome of both physical and cognitive-behavioral treatment in chronic low back pain. J Pain. 2006;7:261–71.

78. Vambheim SM, Kyllo TM, Hegland S, Bystad M. Relaxation techniques as an intervention for chronic pain: A systematic review of randomized controlled trials. Heliyon. 2021;7:e07837.

79. Hassett AL, Finan PH. The role of resilience in the clinical management of chronic pain. Curr Pain Headache Rep. 2016; 20:39.

80. Ferro Moura Franco K, Lenoir D, Dos Santos Franco YR, Jandre Reis FJ, Nunes Cabral CM, Meeus M. Prescription of exercises for the treatment of chronic pain along the continuum of nociplastic pain: a systematic review with meta-analysis. Eur J Pain. 2021;25:51–70.

81. Murphy SL, Lyden AK, Smith DM, Dong Q, Koliba JF. Effects of a tailored activity pacing intervention on pain and fatigue for adults with osteoarthritis. Am J Occup Ther. 2010;64:869–76.

82. Lindstrom I, Ohlund C, Eek C, Wallin L, Peterson LE, Fordyce WE, et al. The effect of graded activity on patients with subacute low back pain: a randomized prospective clinical study with an operant-conditioning behavioral approach. Phys Ther. 1992;72:279–90; discussion 291-273.

83. Elma O, Yilmaz ST, Deliens T, Coppieters I, Clarys P, Nijs J, et al. Do nutritional factors interact with chronic musculoskeletal pain? A systematic review. J Clin Med. 2020;9:702.

84. Vickers AJ, Vertosick EA, Lewith G, MacPherson H, Foster NE, Sherman KJ, et al. Acupuncture for chronic pain: update of an individual patient data meta-analysis. J Pain. 2018;19:455–74.

85. Li LW, Harris RE, Tsodikov A, Struble L, Murphy SL. Self-acupressure for older adults with symptomatic knee osteo-arthritis: a randomized controlled trial. Arthritis Care Res (Hoboken). 2018;70:221–9.

86. Murphy SL, Harris RE, Keshavarzi NR, Zick SM. Self-administered acupressure for chronic low back pain: a randomized controlled pilot trial. Pain Med. 2019;20:2588–97.

87. Smith MT, Haythornthwaite JA. How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. Sleep Med Rev. 2004;8:119–32.

88. Roehrs T, Roth T. Sleep and pain: interaction of two vital functions. Semin Neurol. 2005;25:106–16.

89. Bigatti SM, Hernandez AM, Cronan TA, Rand KL. Sleep disturbances in fibromyalgia syndrome: relationship to pain and depression. Arthritis Rheum. 2008;59:961–7.

90. Irwin MR, Olmstead R, Carrillo C, Sadeghi N, Fitzgerald JD, Ranganath VK, et al. Sleep loss exacerbates fatigue, depression, and pain in rheumatoid arthritis. Sleep. 2012;35:537–43.

91. Abad VC, Sarinas PS, Guilleminault C. Sleep and rheumato-logic disorders. Sleep Med Rev. 2008;12:211–28.

92. Lautenbacher S, Kundermann B, Krieg JC. Sleep deprivation and pain perception. Sleep Med Rev. 2006;10:357–69.

93. Schuh-Hofer S, Wodarski R, Pfau DB, Caspani O, Magerl W, Kennedy JD, et al. One night of total sleep deprivation promotes a state of generalized hyperalgesia: a surrogate pain model to study the relationship of insomnia and pain. Pain. 2013;154: 1613–21.

94. Moldofsky H, Scarisbrick P. Induction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation. Psychosom Med. 1976;38:35–44.

95. Albakri U, Drotos E, Meertens R. Sleep health promotion interventions and their effectiveness: an umbrella review. Int J Environ Res Public Health. 2021;18:5533.

96. Lopez-Martinez AE, Esteve-Zarazaga R, Ramirez-Maestre C. Perceived social support and coping responses are independent variables explaining pain adjustment among chronic pain patients. J Pain. 2008;9:373–9.

97. Cano A, Gillis M, Heinz W, Geisser M, Foran H. Marital functioning, chronic pain, and psychological distress. Pain. 2004;107:99–106.

98. Oraison HM, Kennedy GA. The effect of social support in chronic back pain: number of treatment sessions and reported level of disability. Disabil Rehabil. 2021;43:1526–31.

99. Holtzman S, Newth S, Delongis A. The role of social support in coping with daily pain among patients with rheumatoid arthritis. J Health Psychol. 2004;9:677–95.

100. Heapy AA, Higgins DM, Cervone D, Wandner L, Fenton BT, Kerns RD. A systematic review of technology-assisted self-management interventions for chronic pain: looking across treatment modalities. Clin J Pain. 2015;31:470–92.

101. Keefe F, Caldwell DS, Williams DA, Gil KM, Mitchell D, Robertson C, et al. Pain coping skills training in the management of osteoarthritic knee pain: a comparative study. Behav Ther. 1990;21:49–62.

102. Keefe F, Caldwell DS, Williams DA, Gil KM, Mitchell D, Robertson C, et al. Pain coping skills training in the management of osteoarthritic knee pain-II: follow-up results. Behav Ther. 1990;21:435–47.

103. Keefe FJ, Caldwell DS, Martinez S, Nunley J, Beckham J, Williams DA. Analyzing pain in rheumatoid arthritis patients. Pain coping strategies in patients who have had knee replacement surgery. Pain. 1991;46:153–60.

104. Williams DA, Kuper D, Segar M, Mohan N, Sheth M, Clauw DJ. Internet-enhanced management of fibromyalgia: a randomized controlled trial. Pain. 2010;151:694–702.

105. Murphy SL, Janevic MR, Lee P, Williams DA. Occupational therapist-delivered cognitive-behavioral therapy for knee osteoarthritis: a randomized pilot study. Am J Occup Ther. 2018;72: 7205205040p7205205041–9.

106. Knoerl R, Smith EML, Barton DL, Williams DA, Holden JE, Krauss JC, et al. Self-guided online cognitive behavioral strategies for chemotherapy-induced peripheral neuropathy: a multicenter, pilot, randomized, wait-list controlled trial. J Pain. 2018;19:382–94.

107. Kratz AL, Alschuler KN, Williams DA, Ehde DM. Development and pilot testing of a web-based symptom management program for multiple sclerosis: My MS toolkit. Rehabil Psychol. 2021;66:224–32.

108. Janevic M, Robinson-Lane SG, Murphy SL, Courser R, Piette JD. A pilot study of a chronic pain self-management program delivered by community health workers to underserved African American older adults. Pain Med. 2021. https://doi.org/10.1093/pm/pnaa4

109. Lee YC, Chen PP. A review of SSRIs and SNRIs in neuropathic pain. Expert Opin Pharmacother. 2010;11:2813–25.

110. Mullish BH, Kabir MS, Thursz MR, Dhar A. Review article: depression and the use of antidepressants in patients with chronic liver disease or liver transplantation. Aliment Pharmacol Ther. 2014;40:880–92.

111. Lexi-Drugs/Duloxetine. Lexicomp Online. Waltham, MA: UpTo-Date; 2022 May 18.

112. Williams S, Louissaint J, Nikirk S, Bajaj JS, Tapper EB. Deprescribing medications that may increase the risk of hepatic encephalopathy: a qualitative study of patients with cirrhosis and their doctors. United European Gastroenterol J. 2020; 2050640620975224.

113. Vardeh D, Mannion RJ, Woolf CJ. Toward a mechanism-based approach to pain diagnosis. J Pain. 2016;17:T50–69.

114. Woolf CJ, American College of P, American Physiological S. Pain: moving from symptom control toward mechanism-specific pharmacologic management. Ann Intern Med. 2004;140: 441–51.

115. Handzlik-Orlik G, Holecki M, Wilczynski K, Dulawa J. Osteoporosis in liver disease: pathogenesis and management. Ther Adv Endocrinol Metab. 2016;7:128–35.

116. Rogal SS, Winger D, Bielefeldt K, Szigethy E. Pain and opioid use in chronic liver disease. Dig Dis Sci. 2013;58:2976–85.

117. Chatrath H, Liangpunsakul S, Ghabril M, Otte J, Chalasani N, Vuppalanchi R. Prevalence and morbidity associated with muscle cramps in patients with cirrhosis. Am J Med. 2012; 125:1019–25.

118. Arora A, Rajesh S, Bansal K, Sureka B, Patidar Y, Thapar S, et al. Cirrhosis-related musculoskeletal disease: radiological review. Br J Radiol. 2016;89:20150450.

119. Motoo Y, Taga H, Su SB, Sawabu N. Effect of gegen-tang on painful gynecomastia in patients with liver cirrhosis: a brief report. Am J Chin Med. 1997;25:317–24.

120. Li CP, Lee FY, Hwang SJ, Chang FY, Lin HC, Kuo BI, et al. Treatment of mastalgia with tamoxifen in male patients with liver cirrhosis: a randomized crossover study. Am J Gastroenterol. 2000;95:1051–5.

121. Sikandar S, Dickenson AH. Visceral pain: the ins and outs, the ups and downs. Curr Opin Support Palliat Care. 2012;6:17–26.

122. Wilkie DJ, Huang HY, Reilly N, Cain KC. Nociceptive and neuropathic pain in patients with lung cancer: a comparison of pain quality descriptors. J Pain Symptom Manage. 2001;22: 899–910.

123. Kim KH, Seo HJ, Abdi S, Huh B. All about pain pharmacology: what pain physicians should know. Korean J Pain. 2020;33: 108–20.

124. Amaechi O, Huffman MM, Featherstone K. Pharmacologic therapy for acute pain. Am Fam Physician. 2021;104:63–72.

125. Salduker S, Allers E, Bechan S, Hodgson RE, Meyer F, Meyer H, et al. Practical approach to a patient with chronic pain of uncertain etiology in primary care. J Pain Res. 2019;12: 2651–62.

126. Rakoski M, Goyal P, Spencer-Safier M, Weissman J, Mohr G, Volk M. Pain management in patients with cirrhosis. Clin Liver Dis (Hoboken). 2018;11:135–40.

127. Witenko C, Moorman-Li R, Motycka C, Duane K, Hincapie-Castillo J, Leonard P, et al. Considerations for the appropriate use of skeletal muscle relaxants for the management of acute low back pain. P T. 2014;39:427–35.

128. IASP Terminology. Neuropathic pain. International Association for the Study of Pain; 2017.

129. Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, et al. Neuropathic pain. Nat Rev Dis Primers. 2017; 3:17002.

130. Sene D. Small fiber neuropathy: Diagnosis, causes, and treatment. Joint Bone Spine. 2018;85:553–9.

131. Abbott CA, Malik RA, van Ross ER, Kulkarni J, Boulton AJ. Prevalence and characteristics of painful diabetic neuropathy in a large community-based diabetic population in the U.K. Diabetes Care. 2011;34:2220–4.

132. Chaudhry V, Corse AM, O'Brian R, Cornblath DR, Klein AS, Thuluvath PJ. Autonomic and peripheral (sensorimotor) neuropathy in chronic liver disease: a clinical and electrophysiologic study. Hepatology. 1999;29:1698–703.

133. Chari VR, Katiyar BC, Rastogi BL, Bhattacharya SK. Neuropathy in hepatic disorders. A clinical, electrophysiological and histopathological appraisal. J Neurol Sci. 1977;31:93–111.

134. Dayan AD, Williams R. Demyelinating peripheral neuropathy and liver disease. Lancet. 1967;2:133–4.

135. Kardel T, Nielsen VK. Hepatic neuropathy. A clinical and electrophysiological study. Acta Neurol Scand. 1974;50: 513–26.

136. Knill-Jones RP, Goodwill CJ, Dayan AD, Williams R. Peripheral neuropathy in chronic liver disease: clinical, electrodiagnostic, and nerve biopsy findings. J Neurol Neurosurg Psychiatry. 1972;35:22–30.

137. Seneviratne KN, Peiris OA. Peripheral nerve function in chronic liver disease. J Neurol Neurosurg Psychiatry. 1970;33:609–14.

138. Freynhagen R, Bennett MI. Diagnosis and management of neuropathic pain. BMJ. 2009;339:b3002.

139. Gilron I, Watson CP, Cahill CM, Moulin DE. Neuropathic pain: a practical guide for the clinician. CMAJ. 2006;175:265–75.

140. Themistocleous AC, Ramirez JD, Serra J, Bennett DL. The clinical approach to small fibre neuropathy and painful channelopathy. Pract Neurol. 2014;14:368–79.

141. Krause SJ, Backonja MM. Development of a neuropathic pain questionnaire. Clin J Pain. 2003;19:306–14.

142. Freynhagen R, Baron R, Gockel U, Tölle TR. painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin. 2006;22: 1911–20.

143. Mathieson S, Maher CG, Terwee CB, Folly de Campos T, Lin CW. Neuropathic pain screening questionnaires have limited measurement properties. A systematic review. J Clin Epidemiol. 2015;68:957–66.

144. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain. 2005;118:289–305.

145. Baute V, Zelnik D, Curtis J, Sadeghifar F. Complementary and alternative medicine for painful peripheral neuropathy. Curr Treat Options Neurol. 2019;21:44.

146. Eccleston C, Hearn L, Williams AC. Psychological therapies for the management of chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2015;CD011259.

147. Davies B, Cramp F, Gauntlett-Gilbert J, Wynick D, McCabe CS. The role of physical activity and psychological coping strategies in the management of painful diabetic neuropathy—a systematic review of the literature. Physiotherapy. 2015;101:319–26.

148. Rogal SS, Chinman MJ, DeMonte W, Gibson S, Hoyt-Trapp S, Klima GJ, et al. Using intervention mapping to develop a novel pain self-management intervention for people with cirrhosis. Dig Dis Sci. 2022.

149. Shah NM, Malhotra AM, Kaltsakas G. Sleep disorder in patients with chronic liver disease: a narrative review. J Thorac Dis. 2020;12:S248–60.

150. Zhu HP, Gu YR, Zhang GL, Su YJ, Wang KE, Zheng YB, et al. Depression in patients with chronic hepatitis B and cirrhosis is closely associated with the severity of liver cirrhosis. Exp Ther Med. 2016;12:405–9.

151. D'Mello C, Swain MG. Liver-brain interactions in inflammatory liver diseases: implications for fatigue and mood disorders. Brain Behav Immun. 2014;35:9–20.

152. Bahceci F, Yildirim B, Karincaoglu M, Dogan I, Sipahi B. Memory impairment in patients with cirrhosis. J Natl Med Assoc. 2005;97:213–6.

153. Poynard T, Cacoub P, Ratziu V, Myers RP, Dezailles MH, Mercadier A, et al. Fatigue in patients with chronic hepatitis C. J Viral Hepat. 2002;9:295–303.

154. Bloom A, Mudiyansalage VW, Rhodes A, Hogg M, Jayasekera C, Gorelik A, et al. Can adequate analgesia be achieved in patients with cirrhosis without precipitating hepatic encephalopathy? A prospective study. Clin Exp Hepatol. 2020;6:243–52.