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The assessment and management of pain in cirrhosis

Matthew Klinge[1], **Tami Coppler**[2], **Jane M. Liebschutz**[3], **Mohannad Dugum**[1], **Ajay Wassan**[4], **Andrea DiMartini**[5,6], and **Shari Rogal**[1,6,7,*]

[1]Division of Gastroenterology, Hepatology and Nutrition, University of Pittsburgh

[2]Division of Pharmacy, VA Pittsburgh Healthcare System

[3]Division of General Internal Medicine, University of Pittsburgh

[4]Department of Anesthesiology, University of Pittsburgh

[5]Department of Psychiatry, University of Pittsburgh

[6]Department of Surgery, University of Pittsburgh

[7]Center for Health Equity Research and Promotion, VA Pittsburgh Healthcare System

Abstract

Purpose of review—The treatment of pain in patients with cirrhosis is complicated by unpredictable hepatic drug metabolism and a higher risk of adverse drug reactions. We aimed to conduct a scoping review regarding pain management in cirrhosis.

Recent findings—Despite the high prevalence of pain in patients with cirrhosis, there is little literature to guide the management of pain in this population. Complex pain syndromes and disease-specific pain etiologies exist are common in patients with cirrhosis. There are numerous contraindications and limitations when considering pharmacotherapy for analgesia in cirrhosis, specifically with non-steroidal anti-inflammatory drugs (NSAIDS) and opioid medications. Non-pharmacologic therapies for pain have not been specifically assessed in this population.

Summary—As with other populations, a multi-dimensional treatment approach to pain with a focus on physical, behavioral, procedural and pharmacologic treatment is recommended when caring for patients with cirrhosis and pain. However, more research is needed to evaluate opioid-sparing and non-pharmacologic analgesia in this population.

Keywords

pain; cirrhosis; analgesia; chronic liver disease

[*]Corresponding Author: rogalss@upmc.edu.

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Conflict of Interest

Shari Rogal reports grants from Gilead Sciences, outside of the submitted work.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors

Introduction

Pain is common in patients with liver disease and is difficult to manage. Pain has been found in up to 82% of patients with cirrhosis and is chronic in over half of patients [1•–3]. Patients with more advanced liver disease have an increased prevalence of pain and this is associated with associated sleep and mood symptoms as well as a high risk of pain-related disability and opioid use [1,4–6•]. Despite the high prevalence of pain and its adverse consequences, there is limited guidance on the management on pain in cirrhosis. Given the importance of this topic to patients with cirrhosis, we aimed to conduct a scoping review on the topic of pain management and cirrhosis. We here discuss the assessment and management of pain in patents with cirrhosis with a focus on both non-pharmacologic and pharmacologic treatments and an overall goal of developing a multi-dimensional treatment approach.

Research Methods

A scoping review was done using a MEDLINE search with initial focus on literature published in the past five years addressing overall pain management and evaluation of pain in patients with chronic liver disease. Using a title focused search for “pain” or “analgesics” or “analgesia” or “fibromyalgia” AND “cirrhosis” or “cirrhotic” or “liver” or “hepatic” a total of 122 studies were identified. After critical appraisal and exclusion of studies focused on acute post-operative pain management of hepatic resection or liver transplantation, a total of 10 studies were identified[1,4–12•]. These studies were predominantly descriptive. Given the limited recent data, subsequent MEDLINE searches were done for individual treatment modalities, and historical studies beyond five years were evaluated as needed to complete our review.

The Assessment of Pain in Patients with Cirrhosis

General Principles

The workup of pain is easily overlooked in hepatology clinic given the competing issues requiring attention of the clinician. An evaluation for pain can be accomplished via standard screening assessments, such as numeric or visual analog scales, review of systems or medical interviews based on patient chief complaint. Once identified, the next step is to determine the nature of the pain, including location, quality, and duration and perform a physical examination to assess underlying etiology.

Location: The location of pain guides examination, workup, and treatment. Pain that is localized can be treated with local modalities such as injections or topical treatments and is often easier to address than widespread pain. Often patients with cirrhosis have widespread pain that requires consideration of more systemic processes including inflammation [6].

Quality: Generally pain can be divided into nociceptive and neuropathic types. Nociceptive pain relates to tissue injury and can be classified into somatic and visceral subtypes. Somatic nociceptive pain arises from bone and muscle and is typically localized, while visceral nociceptive pain can be more diffuse. Neuropathic pain is generally burning and tingling in

quality. Other characteristics that should be considered include the frequency of symptoms and relieving and aggravating factors.

Duration: Pain is typically considered to be chronic when it lasts 12 weeks. The approaches to acute and chronic pain differ, so it is critical to assess duration.

Pain related disability and quality of life: Assessing the impact of pain on the patient's function and quality of life is critical to determining the urgency and intensity of treatment. A three-question validated tool, the PEG (Pain, Enjoyment, General activity), can be used. This simple assessment asks about the average pain intensity, pain interference with enjoyment of life, and pain interference with general activity over the past week, all on a scale of 0–10. The 3 scales are averaged for a score from 0–10. The PEG can be administered repeatedly over time to assess for changes in pain function and disability [13,14].

Depression and Anxiety: Depression and/or anxiety often co-occur with chronic pain. Psychiatric disorders are a risk factor for the development of chronic pain but can also be exacerbated by pain-related impairment [15,16]. Depression and anxiety are also implicated in worse clinical outcomes and quality of life in patients with cirrhosis independent of pain [17,18]. Effective treatment of these psychiatric disorders can reduce pain-related impairment in general populations, although this has not been specifically studied in patients with liver disease [19].

Substance Use Disorders (SUDs): Opioid use disorder has been associated with lower pain tolerance [20]. Acute pain has also been associated with increase in relapse to substance use. Thus, understanding the patient's SUD status, including prior history and current use, is essential to devising an appropriate pain treatment plan [21–23•].

Specific Considerations in Patients with Cirrhosis

The majority of patients with liver disease reporting pain describe abdominal pain; however, a large proportion of patients also report pain in the lower back, large joints, and diffusely [1•]. As non-alcoholic fatty liver disease (NAFLD) increases in prevalence, it may overlap with other common non-hepatic painful conditions, such as osteoarthritis related to the common etiological factor of obesity. In addition to the common causes of pain in the general population, cirrhosis itself may exacerbate common non-hepatic painful conditions. For example, cirrhosis-related gynecomastia may cause mastalgia. Other examples of cirrhosis-related pain include:

Abdominal Pain: The high prevalence of abdominal pain in patients with cirrhosis is likely related to several factors including ascites, hepatic capsular distension and splenomegaly [1•, 4,24]. Spontaneous bacterial peritonitis commonly presents with abdominal pain such that any patient with pain and ascites should have a diagnostic paracentesis [25]. Massive splenomegaly in the setting of cirrhosis has been associated with pain that in some extreme cases has even led to partial splenic embolization for symptom control [26]. Another

example of cirrhosis-associated abdominal pain is the visceral hypersensitivity described in patients with HCV [27].

Widespread pain: Cirrhosis is a pro-inflammatory state and the same cytokines associated with cirrhosis are also associated with pain. A fibromyalgia-like syndrome has been found in both HCV and non-HCV related liver disease, which may be related to this systemic inflammation [6]. Thus addressing the liver disease and psychiatric comorbidities with similar pro-inflammatory cytokine profiles is a key component of pain management.

The Management of Pain in Patients with Cirrhosis

General Principles

Similar to treatment of pain in any patient, the pain management plan for patients with cirrhosis should focus on functional outcomes, with particular attention to the most bothersome symptoms for the patient. For severe chronic pain, the treatment plan should be individualized with consideration of physical, behavioral, pharmacological and procedural approaches based on disease stage and etiology of pain [Figure 1]. The treatment of chronic pain can be difficult and is best accomplished with a multidisciplinary approach including behavioral health, palliative care or chronic pain specialists.

Non-pharmacologic pain management

In general, a biopsychosocial approach to pain includes non-pharmacologic options, treatment of underlying psychiatric comorbidities, and an individualized approach. Non-pharmacologic interventions may include a range of options from simple heat and cold therapy and weight loss to more formal treatments such as physical therapy, transcutaneous electrical nerve stimulation (TENS), massage therapy, acupuncture, acupressure, cognitive behavioral therapy, hypnosis and meditation. These modalities have all been described in the palliative care literature as having beneficial effects in the treatment of cancer-related pain [28]. However, there are not data regarding these modalities in patients with cirrhosis specifically. The comparative effectiveness and risks and benefits of these modalities of pain management may differ for this subpopulation and by severity of liver disease.

Physical Treatment

Physical therapy (PT): PT serves a clear role in rehabilitation of acute injuries but can also aid in the management of pain related to chronic conditions like HIV [29]. Sarcopenia and poor physical function in patients with cirrhosis are associated with poor outcomes and PT may help both pain and these associated conditions [30]. Psychologically-based PT, which is more commonly-practiced outside of the US, may be particularly useful in patients with comorbid depression and anxiety [31] and merits further study in patients with cirrhosis.

Weight loss: Studies have consistently shown that weight loss for obese patients improves pain as much as medication [32,33]. Physical activity, which is a part of many weight loss regimens, is also key for maintaining function and muscle strength. Weight loss has the added benefit of treating NAFLD but may not be advisable in patients in the more catabolic phase of cirrhosis.

Behavioral Treatment

Cognitive behavioral therapy (CBT): CBT has been shown to improve pain-related outcomes in general populations and is being actively tailored to manage pain in patients with HIV [34]. CBT is appealing for patients with cirrhosis because behavioral therapy also may address comorbid substance use, depression, and anxiety, which are also associated with pain and poor outcomes in this population [1•].

Mindfulness: A recent large randomized trial showed significant long-term pain reduction in adults with chronic back pain who participated in a mindfulness meditation program [35]. These results were corroborated by a meta-analysis in 2017 that showed a small but significant reduction in pain and depression and improvement in quality of life in patients with chronic pain [36•]. Although not specifically studied in patients with cirrhosis, there is little downside to this approach, though patients with active encephalopathy may not be able to participate in behavioral treatments.

Invasive Procedures

Acupuncture: Acupuncture, including sham acupuncture, has been associated with decreased pain [37]. Although generally considered safe, a systematic review found a wide range of bleeding complications (0.03–38%) such as ecchymosis and hematoma. The disparate risk estimates highlight the need to proceed with caution with expert practitioners, particularly in patients with coagulopathies [38].

Analgesic injections: Nerve blocks and local analgesic injections can positively impact pain in the general population. They should be considered on an individual basis by a pain management specialist, with attention to the increased bleeding risk in advanced cirrhosis.

Pharmacologic pain management

The pharmacological approach to pain management is particularly challenging in patients with cirrhosis due to altered and often unpredictable drug metabolism. The difficulty of pharmacotherapy further supports a more holistic approach to pain in this population. In treating chronic pain, clinicians need to be aware of the potential for addiction with specific medications. This is particularly true of opioid medications and in patients with a history of SUD [23].

Topical Pharmacotherapy—Lidocaine 5% topical patch has been used with success in the treatment of both neuropathic as well as acute and chronic somatic pain syndromes and is a low risk, well tolerated treatment worth consideration in cirrhosis [39,40]. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) have also proven successful in treating muscular skeletal pain in both the acute and chronic settings and have limited systemic side effects when compared to oral NSAIDs [41,42]. However, the safety profile of these medications is unclear in patients with cirrhosis, and this should be evaluated given the dangers of systemic NSAIDS in this population. A systematic review described a moderate efficacy for topical capsaicin in the treatment of both musculoskeletal and neuropathic pain (with the caveat that a topical burning sensation may limit use in some patients) [43].

Systemic pharmacotherapy—The liver is responsible for metabolizing the majority of drugs. Drug metabolism is affected not only by the intrinsic hepatocyte function, but also by hepatic blood flow, drug binding by plasma proteins, and biliary excretion [8,44,45], all which can be affected by cirrhosis. Unlike renal disease where the creatinine clearance provides an accurate reflection of renal function, there is no analogous measure of hepatocyte metabolic function that can be used to predict hepatic metabolism of specific drugs. While the MELD score and Child-Pugh classification predict survival, they are imprecise at predicting dose adjustments given the complex and varied nature of drug metabolism [46,47].

In addition to intrinsic hepatocyte function, other factors affect hepatic metabolism in the context of cirrhosis. Cirrhosis frequently leads to spontaneous portosystemic shunting and sometimes necessitates the intentional creation of a transjugular intrahepatic portosystemic shunt. These shunts further alter hepatic blood flow and can decrease the clearance of drugs relying on first-pass metabolism, leading to higher bioavailability [48]. Furthermore, for highly protein-bound drugs, the decreased albumin production in cirrhosis alters metabolism and elimination. This is compounded by frequent increase in extracellular fluid from edema and ascites that can lead to a significantly increased volume of drug distribution [49].

Hepatic drug metabolism relies largely on oxidation-reduction reactions catalyzed by the cytochrome P450 (CYP) enzymes. These reactions require oxygen and are sensitive to the relative hypoxia induced by shunting [50]. Although P450 isoforms may function relatively well with mild liver disease, a decrease in metabolic activity of all isoforms has been observed in the setting of severe liver disease [51]. Metabolism by glucuronidation seems to be less affected by cirrhosis than oxidation-reduction reactions, possibly secondary to a compensatory increase in extrahepatic metabolism or upregulation of glucuronidation enzymes [52]. Lastly, patients with progressive liver disease are at risk for related renal dysfunction and are thus vulnerable to alterations in renal metabolite excretion. Thus the metabolism of medications in the context of cirrhosis is complex. Predicting the overall effects of the disease on drug metabolism requires an understanding of the metabolism of individual drugs as well as an assessment of each patient's renal function, volume of distribution, and presence of portosystemic shunting. Future research should aim to create models to predict safe dosing of medications for individual patients.

Acetaminophen (Paracetamol)—Although commonly used by the general public for analgesia, acetaminophen is frequently avoided in patients with liver disease out of fear for its well-known often-fatal hepatotoxicity in high doses. However, although limited data exist regarding chronic daily acetaminophen, a reduced dose of 2g/day is generally considered safe in patients with cirrhosis [8,44,45]. Acetaminophen is predominantly metabolized by glucuronidation and sulfation with 5% undergoing oxidation by CYP to the hepatotoxic compound N-acetyl-p-benzoquinone imine (NAPQI). NAPQI requires glutathione for detoxification which can be depleted in the setting of chronic alcohol use but has been found to be relatively preserved in patients with cirrhosis [53]. Supporting this is a double-blind study in which 20 patients with chronic liver disease (of undocumented severity) were treated with acetaminophen 4g/day or placebo for 13 days followed by crossover to the alternative treatment for 13 days with no resultant significant changes in laboratory tests

[54]. Thus low-dose acetaminophen (≤2gm/day) is considered to be a first-line analgesic for patients with cirrhosis.

Nonsteroidal Anti-inflammatory Drugs (NSAIDS)—Given perceived concerns about acetaminophen use, patients with cirrhosis are often given NSAIDS as a “less toxic” alternative, when in fact NSAIDS are likely more dangerous in this population. NSAIDs are predominantly metabolized by CYP enzymes and are heavily protein-bound. Patients with cirrhosis rely on renal prostaglandin activity to maintain adequate renal perfusion, but NSAIDs inhibit prostaglandin production, which leads to decreased GFR, rise in creatinine and decreased natriuresis [55,56]. Furthermore, NSAIDs increase the risk of bleeding via inhibition of thrombaxane A2 production by platelets. One case-control study found an association between NSAID use and variceal bleeding (OR=2.9) [57]. Given these significant risks, NSAIDS are contraindicated in patients with cirrhosis. Patients with cirrhosis should be educated about safe and unsafe over-the-counter analgesia since there is often confusion among both providers and patients regarding the relative safety and danger of these medications.

Opioids

The well-publicized dangers of opioid use in the general population may be magnified in the context of cirrhosis [58••,59]. Chronic liver disease is a risk factor for prescription opioid overdose and toxicity and opioid use has been associated with adverse transplant outcomes [60–63•]. A history of substance abuse is common in patients with cirrhosis and prescription opioids can lead to addiction, particularly among those with history of addiction. In general opioids should be avoided to the extent possible in this population. One notable exception is the hospice/end-of-life setting, where the risk-benefit profile of these medications is changed.

Opioids have well-established side effects of respiratory suppression, sedation and constipation, which can lead to new or worsening hepatic encephalopathy if not managed carefully [64•]. Given the established relationship between opioids and encephalopathy, which may be in part mediated by constipation, it is reasonable to provide lactulose and/or rifaximin to all patients taking opioids[45].

When prescribing opioids, it should be in conjunction with the guidance of a chronic pain and/or palliative care specialist. When prescribing opioids *for any patient*, the CDC recommends a short duration of <7 days for acute pain since longer prescriptions are rarely needed and increase the addictive potential [58]. The decision to use opioids for the treatment of chronic pain is difficult and should only be done when non-opioid treatment options have been exhausted and the potential gain in patient function and quality of life is felt to outweigh the significant risks of long-term opioids.

The “safe” limits of opioids have yet to be established in the context of cirrhosis and are likely even lower than the general population. Doses >50 MME per day have been associated with increased overdose risk in general population [65]. However, pre-transplant opioid doses as low as 10 MME per day, were associated with significant increases in post-transplant mortality in one study [61•]. Sustained release opioids should be avoided because

of the risk of drug accumulation in cirrhosis. Similarly, due to the risk of acetaminophen toxicity with combination pills, combination opioid-acetaminophen pills should be avoided in patients with cirrhosis. The metabolism and data regarding the different opioid types are outlined below.

Oxycodone: Oxycodone is metabolized by CYP to the active metabolite oxymorphone. This reliance on metabolism to the active metabolite may again reduce its analgesic efficacy in the context of cirrhosis [66]. Given the fluctuations in drug concentration, increased half-life and unpredictable blood levels of oxycodone in patients with liver disease, it is not the drug of choice in patients with cirrhosis [44,67].

Morphine: Morphine does not rely on CYP metabolism but undergoes significant first-pass metabolism via glucuronidation. Glucuronidation is affected by decreased hepatic blood flow leading to increased oral bioavailability in the setting of impaired hepatic function [68]. One neurotoxic metabolite of morphine, normorphine, can precipitate seizures when renal clearance is decreased and thus morphine should not be used in patients with renal dysfunction [69].

Hydromorphone: Unlike the aforementioned opioids, hydromorphone does not require metabolism to an active analgesic metabolite. Similar to morphine, hydromorphone undergoes high first-pass metabolism via glucuronidation, which is again decreased in the setting of cirrhosis leading to a higher oral bioavailability [70]. In a pharmacokinetic study conducted in patients with moderate hepatic impairment, even though the maximum drug concentration was increased after a single dose of hydromorphone, reduced hepatic function did not have any effect on the elimination of hydromorphone [70]. The metabolites of hydromorphone are generally considered to have minimal neurotoxicity and it is frequently the opioid of choice in the context of renal and hepatic dysfunction [45].

Fentanyl: Fentanyl is metabolized by CYP with a high rate of hepatic extraction suggesting that clearance would be decreased by decreased hepatic blood flow [71]. However, when studied in patients with well-compensated cirrhosis and preserved hepatic blood flow, the pharmacokinetics of a single intravenous dose in these patients were similar to those of healthy controls [72]. These results cannot be extrapolated to decompensated cirrhosis or transdermal use. The manufacture label states there is a change in fentanyl patch area under the curve (AUC) from 35% in controls to 73% with liver disease and as a result the patch should be avoided in “severe hepatic impairment” [73].

Tramadol: Metabolized by CYP to an active metabolite that has a low affinity for opioid receptors, tramadol has been historically considered to be less sedating and addictive then other opioids [74]. In the setting of cirrhosis, the metabolism of tramadol can be decreased as liver disease progresses, which may reduce the formation of the active metabolite and decrease the analgesic effects in a manner similar to patients with poor intrinsic metabolizing ability [75,76]. Tramadol lowers the seizure threshold and should not be used in patients with a seizure disorder or in combination with selective serotonin reuptake

inhibitors, anticonvulsants or tricyclic antidepressants given the risk of serotonin syndrome [77]. More research is needed to establish the safety of tramadol in patients with cirrhosis.

Buprenorphine—Metabolized by CYP to an active metabolite that is eliminated via glucuronidation with biliary excretion again necessitates dose reduction and slow up titration of buprenorphine in the setting of chronic liver disease [78]. The active metabolite is a weak mu-opioid receptor agonist but with high binding affinity. This property can cause displacement of other circulating opioid agonists and has led to combination formulations with a theoretical decreased risk of overdose and adverse effects [79]. A recent review concluded that bupreinorphine has similar efficacy for pain reduction when compared to other opioids but further study is needed in general populations [80]. This medication requires hepatic metabolism and more data are needed in patients with cirrhosis.

Methadone—Methadone is a synthetic opioid with a long half-life. It is frequently used in the treatment of opioid use disorders but is also used for chronic pain. Methadone is metabolized by the CYP system and limited studies suggest that drug clearance is not altered by liver disease or renal impairment and thus dose adjustment is not theoretically necessary [81,82]. However, while this made methadone an attractive analgesic for patients with liver disease in the past, its long half-life can lead to accumulation over time which has decreased its use for pain management in the context of liver disease.

Anticonvulsants

Anticonvulsants including gabapentin and pregabalin serve a prominent role in the treatment of neuropathic pain. Gabapentin and pregabalin bind to voltage gated calcium channels in the CNS and undergo minimal hepatic metabolism with unchanged drug excretion from the kidney [83]. Gabapentin has no convincing reports of significant hepatotoxicity, and is subsequently been a first-line agent for the treatment of neuropathic pain with a maximum does of 3600mg/day assuming normal renal function [84]. Pregabalin does have rare reports of idiosyncratic liver injury and should thus be used as a second line agent [85]. While carbamazepine is used for neuropathic pain, hepatotoxicity and drug reaction with eosinophilia and systemic symptoms (DRESS) has been well described with this drug and its use in cirrhotic patients should be avoided [86]. Carbamazepine can also induce bone marrow suppression, which is also already a concern among patients with cirrhosis. Gabapentin and pregabalin are both reasonable first line medications for the treatment of neuropathic pain. However, they can cause sedation and have addictive potential so the doses should again be slowly up-titrated with preferential dosing before bed.

Antidepressants

Neuropathic pain can be difficult to treat and antidepressants have also been frequently used with moderate success. Nearly all classes of antidepressants have been implicated in idiosyncratic drug-induced liver injury to some extent, although this is a rare clinical outcome [87]. Tricyclic antidepressants (TCAs) are commonly used for the treatment of neuropathic pain and are metabolized by CYP enzymes and rely on renal elimination and as such drug accumulation can be seen in progressive liver disease. Nortriptyline and desipramine are preferred to amitriptyline, imipramine and doxepin as they appear to have

less anti-cholinergic and sedating effects. However, all TCAs have the potential to induce or exacerbate encephalopathy and have fatal overdose potential so their use is generally not recommended in the context of liver disease [88].

Serotonin-norepinephrine reuptake inhibitors (SNRIs) including venlafaxine and duloxetine have also been used in the treatment of neuropathic pain but are likely not good options for patients with cirrhosis. Duloxetine carries a manufacture warning of hepatotoxicity given its implication in numerous cases of drug-induced liver injury and is not recommended in patients with chronic liver disease [89]. Venlafaxine relies heavily on hepatic CYP metabolism necessitating significant dose reduction if it is used [90].

Selective serotonin reuptake inhibitors (SSRIs) are not recommended for the treatment of neuropathic pain in general populations as they have a lower efficacy compared with TCAs and also pose an increased risk of GI bleeding [91,92]. However, given the risks of TCAs in this population, SSRIs are often used, though more work is needed to determine the effectiveness of SSRIs for chronic pain in this population.

Cannabis

While there is growing interest regarding the efficacy of cannabis for treating pain in general populations, the safety profile of cannabis in cirrhosis requires more research. For example, an initial cross-sectional study suggested an association between daily cannabis use and liver fibrosis [93]. More recently, however, a prospective cohort study of 690 HIV-HCV co-infected patients without liver fibrosis at baseline found no association between self-reported cannabis use and subsequent development of hepatic fibrosis, although the median follow-up was limited at 2.7 years [94]. Certainly cannabis use poses difficulties in a patient population with a high prevalence of addiction, and variable transplant policies around marijuana and transplantation exist. Additionally, most studies of the medicinal efficacy of cannabinoids assessed pharmaceutical medications dronabinol and nabilone, not smoked cannabis [95]. More research on the effects and proper patient selection is needed before medicinal cannabis can be recommended.

Conclusions and Recommendations

Pain is common in cirrhotic patients and can vary in location and presentation. We recommend that an assessment of pain symptoms, comorbid conditions, function and disability be a routine part of clinical care, recognizing that this can be challenging when faced with competing needs to address the many medical consequences of cirrhosis.

All pain treatment should progress in a step-wise fashion with an increasing focus on non-pharmacologic low-risk treatment interventions. Attention to comorbid conditions such as depression, anxiety and substance abuse represent separate but exceedingly important treatment targets in a multi-dimensional treatment approach (Figure 1) [96].

In terms of pharmacotherapy, NSAIDS and other hepatotoxic medications should be avoided. Opioid use should be limited and avoided to the extent possible, given both the lack of efficacy in the context of chronic non-malignant pain and the potential of opioids to

causing encephalopathy, addiction and overdose. If opioids are used, it is critical to maintain the lowest possible dose with the goal to use opioid-containing medications for <7 days if at all. Sustained release oral preparations and combination medications should be avoided. The data on the safety of transdermal fentanyl in cirrhosis suggests that it should be avoided. Hydromorphone may be a reasonable first line opioid agent given its short half-life, lack of hepatic metabolism to an active analgesic metabolite and absence of neurotoxic metabolites. Lactulose should be started empirically to avoid constipation and prevent hepatic encephalopathy when using psychoactive medications. Overall, opioids are to be avoided for chronic management of pain in this population and other approaches should be used. More research is urgently needed to guide the management of pain in patients with cirrhosis.

Directions for Future Research

Future research should address non-pharmacologic treatment of pain for patients with cirrhosis with a focus on a multi-dimentional model of care. More work is also needed to understand the comparative effectiveness and risks associated with the use of various analgesic medications in this population. Safety thresholds for different opioids should be established for patients with cirrhosis in order to help decrease the risks of opioids for those already taking them. Implementation research should focus on increasing the uptake of opioid-sparing medications and approaches. Personalized medicine approaches can be considered to predict effectiveness and safety of medications.

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96. Figure modified from "Boston University School of Medicine SCOPE of Pain" presentation slide.

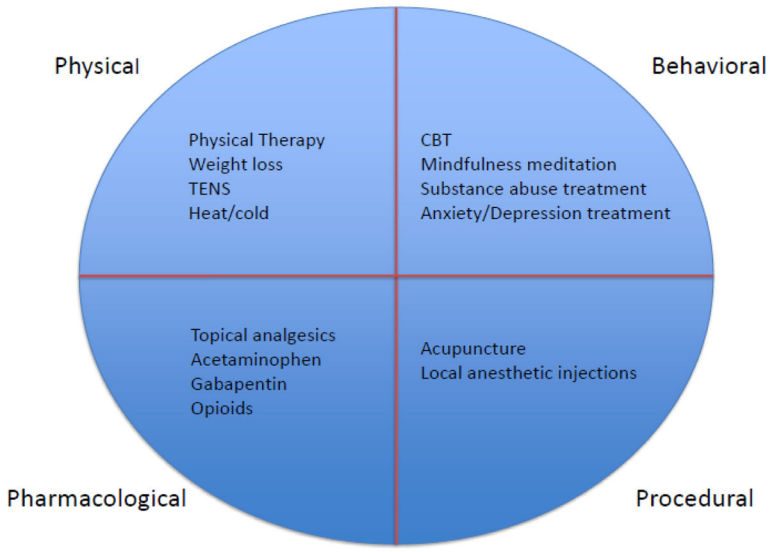

Figure 1.
Pain Management in Cirrhosis: Multi-dimensional Treatment Approach