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Literature Review

Pain Management in Patients with Hepatorenal Syndrome: A Literature Review

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Abstract

Introduction: Patients with cirrhosis often present with pain as a common complaint. Pharmacological pain management safety depends on the excretion and metabolism of drugs by the kidney and the liver. The analgesic choice in cirrhotic patients can be tremendously challenging, especially in patients with hepatorenal syndrome, a potentially reversible renal impairment associated with an increased drug accumulation and a high risk of potential toxicity. Choice and dose of medications depend on various factors, including the severity of the condition, possible drug interactions, drug dependence, and liver transplant status. Ideally, medications should be titrated from the lowest effective dose to higher strength. This review aims to discuss the pharmacodynamic and pharmacokinetics of analgesics used in cirrhotic patients. The metabolism of each drug, route of administration, pathophysiology, and limitations of their use are discussed to better understand their implementation in patients with cirrhosis and HRS. For this purpose, we performed a systematic literature search in PubMed and Google Scholar. Articles were searched via search terms and keywords. Certain high potency opioids like Sufentanil, Fentanyl, Remifentanil, Oxymorphone, and Butorphanol can be used cautiously. Low potency opioids such as Pentazocine, Tramadol, Nalbuphine, and Tapentadol may also be considered with dose adjustments. Albeit less favorable, some other analgesic options include Gabapentin, Pregabalin, acetaminophen, Duloxetine, Venlafaxine, Fluoxetine, Topical Lidocaine, Capsaicin, and Clonidine.

Methodology: A systematic literature search in PubMed and google scholar was conducted between March 5 and August 10, 2021. Articles were searched via search terms and keywords relating to *International Classification of Diseases*: hepatorenal syndrome, pain, opioids, metabolism, renal clearance.

Results: One thousand three hundred eighty-seven articles were identified from database searching. After removal of duplicates, 924 studies were screened for eligibility. After review of titles and abstracts, 665 studies were rejected for relevance reasons. Most of these studies were rejected because they were not relevant, did not meet search criteria, case-control article, case series articles, no English translation, articles did not mention adjustments in patients with liver or kidney disease. One hundred forty-two articles were used for the synthesis.

***Keywords:** Pain; hepatorenal; opioids.*

Introduction and Background

High potency opioids

Sufentanil

Sufentanil is a highly-protein-bound potent synthetic lipophilic opioid that is extensively metabolized by the liver. Administered intravenously, intramuscularly, subcutaneously, intrathecally, or epidurally. Single-dose pharmacokinetics is not significantly altered in patients with cirrhosis, although the impact of continuous infusions and reduced protein binding can prolong the effect [12].

Biotransformation occurs through N-dealkylation, oxidative de-ethylation, oxidative demethylation, and aromatic hydroxylation [13]. Pharmacokinetics are characterized by a short onset of action and a rapid increase in plasma concentration after bolus administration. In addition, sufentanil is rapidly eliminated; after an injection of 3 μg/kg, 98% of the amount injected was no longer detected in plasma after 30 min [14]. In a matched-pair analysis, the authors were able to show that the kinetics of a single dose of 3 μg/kg sufentanil in 12 patients with liver cirrhosis were not altered compared to healthy patients [15]. This drug has no active metabolites and is generally not expected to require dose adjustment in the presence of renal impairment [16]. Sufentanil can be used in patients with hepatorenal syndrome in a single dose and infusions. Regarding infusions, patients should be monitored cautiously [12].

Fentanyl

Fentanyl is a highly fat-soluble, potent narcotic and analgesic, the effect of which is maximally pronounced after 2-4 minutes when administered intravenously. Fentanyl is highly bound (85%) to plasma proteins. It is eliminated to a high degree when it passes through the liver (hepatic extraction rate 0.8-1.0); approximately 60% of the substance is metabolized in the first passage. In the liver, conversion to inactive metabolites [4-N- (N-propionylanilo) piperidines and 4-N- (N -hydroxypropionylanilo) piperidines]. These inactive metabolites are then renally excreted. The short duration of action depends on concentration, so repetitive doses lead to higher plasma levels and a longer duration of action [17]. According to current research, the resulting metabolites may accumulate but are inactive and non-toxic [17]. The cytochrome P3A4 system is mainly involved in the metabolism of fentanyl.

With adequate hepatic blood flow, the high hepatic extraction rate means that sufficient substance is broken down even with reduced enzyme activity. In a study on eight patients with low-grade liver cirrhosis, no significant changes in the pharmacokinetics of fentanyl regarding half-life, plasma clearance, and volume of distribution were found compared to control patients [18]. Therefore, no dose adjustment is necessary for a single bolus administration in patients with hepatorenal syndrome. In the case of a transdermal patch, the recommendation of only 50% of the initial dosage. In repeated administration, continuous infusion, or high doses, accumulation may result in a prolonged duration of action. Recommend to proceed with caution [19].

Alfentanil

Alfentanil is an ultra-short-acting opioid with a rapid onset of action of 5 minutes with an effect lasting about 30-60 minutes. Approximately 88-92% binds to alpha-1 acid glycoprotein. Compared to fentanyl, alfentanil is less potent, with a smaller distribution volume and shorter half-life. The drug has no significant active metabolites. Alfentanil is characterized by a relatively low hepatic extraction rate (0.3-0.5) and is eliminated almost exclusively through the liver. Alfentanil is enzymatically dealkylated and demethylated in the hepatocytes, including CYP3A4. Only 1% passes through the kidneys unchanged and is excreted in the urine [18]. Alfentanil is metabolized by the cytochrome P450 (CYP) enzyme 3A4, the most common CYP enzyme in the human liver, and is involved in the metabolism of more than 50% of the drug. Therefore, like all drugs metabolized by this pathway, their levels can be influenced by many other medicines, which can accelerate or delay their metabolism. Meaning, that the effect of alfentanil should be closely monitored in terms of analgesia and toxicity [20]. In patients with ethyl-toxic liver cirrhosis, the plasma clearance after alfentanil bolus administration of 50 μg/kg was significantly lower than in healthy volunteers. In addition, elimination of half-life and a free fraction of the drug in the plasma was increased in liver cirrhosis. Ashley et al. observed a lower significant plasma clearance of alfentanil in cirrhosis groups than in the control group. Based on these data, alfentanil does not seem recommended if hepatic metabolism is impaired [21,22]. Alfentanil is not recommended for use in patients with hepatorenal syndrome.

Remifentanil

Remifentanil is an ultra-short-acting synthetic drug and also a powerful agonist for μ receptors [23, 24]. It is available in the form of an intravenous drug. Unlike other opioids, Remifentanil has no hepatic metabolism [24]. Remifentanil is a synthetic opioid with an ester linkage that allows for rapid hydrolysis by blood and tissue esterases; such hydrolysis leads to high clearance, rapid elimination, and recovery that is almost independent of the dose or duration of infusions [25]. The duration of action of remifentanil has been found to be short, even in patients with renal or hepatic impairment [26]. Predictably, the clearance and elimination of remifentanil are unchanged in patients with severe liver disease or in those undergoing liver transplantation [10,27]. In renal insufficiency, the pharmacokinetics of remifentanil do not change, although the half-life of its metabolites is slightly prolonged [28] Remifentanil is therefore a safe drug for patients with impaired kidney function. Remifentanil is recommended for use in patients with hepatorenal syndrome at the usual dose [29].

Buprenorphine

It is a partial mu-opioid receptor agonist and weakly antagonist at kappa and delta opioid receptors. Buprenorphine is one of the opioids approved for use as an alternative to methadone in the treatment of opioid dependence. In addition, it has also been used to control chronic pain. Because of its lipophilic nature, it has a high affinity and slowly dissociates from the mu-opioid receptor, resulting in a long duration of analgesic effect. It is metabolized through the liver by oxidation into its active metabolite norbuprenorphine by CYP450 enzyme (VYP3A4), which is then glucuronidated. It has a high protein binding affinity of approximately 96%, mainly alpha and beta globulin [30]. Sublingual, transdermal, IM and oral formulations are the most common of administrations available. It undergoes high first-pass metabolism through oral route leading to 15% of bioavailability which is not enough to control pain, therefore this route of administration is not preferred. It begins to act in less than 5 minutes by the sublingual (SL) route. Bioavailability is 30% by SL, 70% by IM and 15% by transdermal. Transdermal formulation maintains therapeutic blood levels over a longer period hence providing longer pain control. Approximately 80 to 90 % of its elimination is by stools and 10 to 20 % by urine. There is also an enterohepatic recirculation that leads to the prolongation of its T ½. When GFR is lower, 10 ml/min, reduce the dose by 50% [30,31]. Unfortunately, no studies on buprenorphine are currently not available to determine whether the dose needs to be adjusted or whether the pharmacokinetics remain unchanged in hepatic impairment. Cases of hepatitis have been reported with buprenorphine use in patients with pre-existing liver dysfunction [32]. For these reasons buprenorphine should be used cautiously in patients with hepatic disease. It is not recommended for use in patients with hepatorenal syndrome.

Methadone

It is metabolized by CY3A4 and 1A2 enzymes in the liver, so its clearance decreases in patients with severe hepatic insufficiency. It is excreted by faeces after transformation into inactive metabolites. Methadone is used to control severe pain, detoxification, and temporary treatment of drug dependence. It is available in oral, parenteral (IV, IM), suppositories, inhalation, and subcutaneous forms. Oral formulation is commonly used, with a half-life of 8 to 60 hours. The analgesic duration of methadone is 2 to 6 hours after the first dose and 3-6 hours after the repeated dose [33]. It has high protein binding affinity but has no toxic metabolites therefore it is best tolerated by patients with hepatic impairment [31]. Reduced doses are needed in patients with hypoalbuminemia, as the methadone is strongly protein bound. Because the kidney is not involved with elimination, it can be safely used in patients with kidney disease. However, for patients with RFG<10, it is advised to start with lower doses and titration gradually until the desired pain control is achieved [33]. While taking this medication, patients should look out for common side effects such as dizziness, constipation, forgetfulness, and impaired cognition, or confusion. The use of methadone for analgesia and not as maintenance treatment in patients with hepatic impairment has not been investigated. The disposition of methadone appears to be relatively unaffected in renal impairment, thus its clearance should not be further reduced in the presence of hepatorenal syndrome [34]. However, due to the significant inter-individual variability of methadone pharmacokinetics and its long t1/2, this drug should not be used as a first-line analgesic treatment in patients with liver disease. However, although methadone is an attractive analgesic for patients with liver disease, its long half-life may lead to accumulation, which has reduced its use for pain management in severe liver disease [35]. Methadone is contraindicated in patients with severe liver diseases. We do not recommend it in patients with type 1 hepatorenal syndrome. Use cautiously in patients with HRS type 2.

Oxymorphone

Oxymorphone is a narcotic analgesic used to treat moderate to severe pain. Oxycodone is partially metabolized by cytochrome P450 2D6 into oxymorphone. However, oxymorphone has a significantly longer half-life of approximately 7-9 hours than oxycodone, with an average elimination half-life of 3.51 hours in one oral dose [36]. It is highly metabolized, mainly in the liver, and undergoes reduction or conjugation with glucuronic acid. Less than 1 % is excreted unchanged in the urine [16]. The drug has a rapid onset of action (as it is more lipid soluble than morphine), and duration of action is approximately 4-6 hours [16]. It can be given as oral, IV, IM or SubQ. In patients with creatinine clearance below 50mL/min, start with the lowest dose of 5 mg and slow titration (naïve opioid patients). Doses IV, IM and subcutaneous should be reduced and slowly titrated in the case of renal failure. The same dose reduction should be followed in the event of hepatic dysfunction [37]. The extended release of oxymorphone is no longer produced and it has been replaced by oxycontin (oxycodone extended release). Oxymorphone can be used in patients with hepatorenal syndrome, with appropriate dose adjustment and with a close follow-up by an expert in pain management.

Butorphanol

Butorphanol is a kappa opioid receptor and a partial opiate mu receptor agonist. It is metabolized hepatically to hydroxy butorphanol. It's action peaks at around 0.5-1 hour (IM and IV) and 1-2 hours nasally. The drug can be administered IM, IV or intranasally [38]. The drug is 80% protein bound and is absorbed rapidly. It takes about 20-40 minutes to reach peak when given IM and 30-60 minutes when it is given nasally. The effects of the drug last about 3-4 hours when given IM and 4-5 hours when given intranasally. The drug is excreted mainly in urine (70-80%) and faeces (15%) [39]. The elimination half-life is approximately doubled, and the total body clearance is approximately one half in patients with creatinine clearance below 30 mL/minute. The elimination half-life is approximately tripled, and the total body clearance is approximately one half in the case of hepatic dysfunction. The drug is mainly metabolized in the liver, with extensive first-pass metabolism, resulting in oral bioavailability 5-17% [36]. Repeated doses should be in accordance with the initial dose in patients with hepatorenal syndrome. This medication can be used cautiously.

Hydromorphone

Hydromorphone is a semisynthetic opioid that undergoes important first-pass metabolism, resulting in low oral bioavailability [40]. It is primarily metabolised by glucuronide conjugation to hydromorphone-3-glucuronide. Several other metabolites are formed in smaller amounts: hydromorphone-3-glucoside, dihydromorphine, and unconjugated and conjugated dihydroisomorphine. In patients with moderate hepatic impairment, Cmax and AUC increased 4 times after administration of a single dose of oral immediate release hydromorphone. This increase was probably a consequence of reduced first-pass metabolism. The t1/2 of the drug in patients with hepatic impairment was equal to that of controls [41]. Based on the results, a reduction of hydromorphone dose with maintenance of the standard dosing interval is necessary in patients with moderate liver disease. Possible decreases in the metabolizing capacity of conjugating enzymes with the advancement of liver disease may lead to an increase in the t1/2 in patients with severe liver disease. However, no studies investigating the pharmacokinetics of hydromorphone in patients with severe liver disease are currently being undertaken. In the presence of renal impairment, an accumulation of the neuroexcitatory metabolite hydromorphone-3-glucuronide has been observed. [42,43,44]. Therefore, hydromorphone should be avoided in patients with hepatorenal syndrome.

Oxycodone

Oxycodone is a semisynthetic mu opioid agonist that has pharmacodynamic potency similar to morphine. Compared with morphine, oxycodone displays similar protein binding capacity but a higher oral bioavailability (60-87%). The metabolism of oxycodone depends on oxidative enzymes, including CYP3A4 and CYP2D6, which transform oxycodone to noroxycodone and the active metabolite oxymorphone, respectively [31,45-47]. An impairment in oxycodone metabolism in liver disease might occur because of decreased hepatic blood flow and/or decreased intrinsic clearance, since the metabolizing activity of oxidative enzymes is reduced in chronic liver disease. In this case, the formation of the active metabolite oxymorphone would be reduced, resulting in potentially lower analgesic effects as observed in poor CYP2D6 metabolizers [11, 48, 49]. In advanced hepatic impairment, the maximum concentration of oxycodone increases by 40% and the immediate-release oxycodone half-life increases to 4.6-24.4 hours (average 14 hours; its usual half-life is ~3.5 hours) [50]. Initial doses of oxycodone in patients with severe hepatic failure should be reduced to 30%-50% of the recommended starting dose. It is recommended to initiate therapy with lower doses and extended intervals, allowing for adequate time between doses to avoid accumulation and titration according to the patient's response. The oxycodone dosage for healthy patients whose opioid tolerance has been established is a single dose of 60mg per day [50]. However, patients who have kidney disease should take a maximum of 20 mg in a day. This is also the case for patients with liver disease. Like the previous drug, oxycodone undergoes zero-order kinetics where a constant amount of the drug is eliminated independently of the concentration [51,52]. The drug is meant to stay in the body for a specific time after which it is excreted. Oxycodone has increased oral bioavailability due to decreased first-pass effect and t 1/2 prolongation due to significant protein binding, which increases the risk for toxicity. Avoid ER formulations (oxycodone ER [OxyContin, Xtampza ER]) in patients with hepatorenal syndrome [16]. It may be used in patients with renal failure if closely monitored but is considered a second-line agent both parent compound and metabolites are substantially renally excreted; oxymorphone, and oxycodone metabolite, and the parent compound accumulate in renal failure; dose adjustment is recommended [38].

Low potency opioids

Pentazocine

Pentazocine, also known as narcotic, is an opioid medication for pain. This narcotic is used to treat moderate to severe pain in people older than 12 years. It can also be used in surgery as anesthesia. Pentazocine administration route is by injection intravenous, intramuscular, and subcutaneous [53]. Oral administration of pentazocine has less predictable response but is able to provide a similar degree of analgesia as compared to parenteral pentazocine [54].

The metabolism of pentazocine may differ between different patients. However, the average metabolic process of pentazocine is undergoing an extensive first-pass metabolism in the liver. After this process, the drug passes into the systemic circulation. The lipophilic nature of pentazocine helps them to get to their target tissues by crossing the cell membranes. The main site for the metabolism of pentazocine is the liver. The drug is also subject to zero-order kinetics where a constant amount of the drug is eliminated regardless of the concentration.

In patients with liver disease because of lower clearances and longer half-lives, pentazocine should be used and the dosage adjusted carefully. The bioavailability of pentazocine is greater in the cirrhotic compared to normal subjects. The increased bioavailability in the cirrhotic patients is a result of the lower first pass clearance after an oral dose of each drug, probably due to loss of hepatic enzyme activity and decrease in effective liver blood flow. The recommendation of Pond et al is that patients with severe liver disease receive 10-25% of the usual oral dose of pentazocine, because its half-life is approximately double in cirrhotic patients. Otherwise, for multiple parenteral injections, the dosing interval would have to be doubled, or the doses reduced by approximately 50%, because of the decreased systemic clearance and prolonged half-life of the drug [55]. It can be used in patients with hepatorenal syndrome decreasing the dosage and increasing the intervals of the medication.

Meperidine

Meperidine is a synthetic opioid with weak addictive properties compared to morphine. T1/2 is 2 to 4 hours and binds to 70% protein [47,56]. Meperidine is converted to norpethidine through methylation, and pethidine acid through hydrolysis via CYP2B6 and CYP3A4. Norpethidine is responsible for 50% of the analgesic effect of Meperidine and has its effect on μ-opioid receptors. It is excreted primarily by the kidney in the form of glucuronic acid [57]. This pharmacodynamic is impaired in cirrhosis with or without renal insufficiency, particularly with repeated dose, due to decreased drug clearance and/or increased oral bioavailability, at repeated doses [47]. Although meperidine production decreases in patients with cirrhosis with liver function impairment, the cumulative effect is the reason behind increased toxicity. Most common side effect noted is seizure and neurotoxicity, which is seen even at lower dosage in these patients [57]. Due to increased bioavailability of CNS toxic metabolite and increased bioavailability (T1/2 being 15-30 hours), Meperidine can precipitate hepatic encephalopathy and therefore should be avoided in patients with liver and renal issues [47,56]. Meperidine should not be used with MAOI as it induces hyperpyrexia along with seizure delirium, respiratory depression, and neurotoxicity [58].

Codeine

Codeine is a weak opioid analgesic and has a low affinity with μ opioid receptors. Codeine is also called 3-methylmorphine as it is converted to Morphine, an active metabolite, by the CYP450 system (CYP2D6) and glucuronidation [32]. Codeine induced liver injury and hepatic DNA damage via caspase 3-dependent signaling by suppressing hepatic antioxidant status and enhancing free radical and TNF-α generation [56,57]. 90% of metabolites are excreted by the kidney and 10% by feces [47]. Due to impaired metabolism in hepatic failure patients, the analgesic effect of codeine is very unpredictable [32,47]. Moreover, due to the accumulation of its active metabolites, codeine can cause respiratory depression in these patients [31]. Therefore, codeine should be avoided in patients with hepatorenal syndrome and seek alternative medication.

Dihydrocodeine

This probably has similar elimination to codeine, and has been reported to cause prolonged sedation, reversible with naloxone. It has not been so intensively studied however and should be avoided in the presence of renal failure [17, 59]. No evidence was found to guide treatment in the presence of hepatic dysfunction. We do not recommend in patient with hepatorenal syndrome.

Morphine

Morphine is metabolized by glucuronidation to two major metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). M6G is an active analgesic that is more potent than morphine, while M3G has no analgesic effect but contributes to neurotoxic side effects such as confusion. Morphine accumulation has been reported in liver disease which can result from decreased plasma clearance and/or increased elimination half-life of the parent drug [60]. The metabolism of morphine is impaired significantly in patients with severe cirrhosis. Clinically significant results were high oral bioavailability and long elimination half-life. These results require a cautious oral and intravenous morphine in patients with severe end stage liver disease [61,62]. Morphine should be avoided in patients with hepatorenal syndrome due to increased risk of neurotoxicity resulting from morphine-3- glucuronide and morphine 6-glucuronide accumulation in severe renal impairment [31].

Tramadol

Tramadol undergoes more than 80% of liver metabolism. The biotransformation of tramadol to its main metabolite, O-demethyl tramadol, is catalyzed by CYP2D6. Tramadol is characterized by a dual mechanism of action: modulation of the central monoaminergic pathways and m-opioid receptors agonist. Tramadol may be beneficial in intractable pain due to partial inhibition of serotonin reuptake [31,63]. Tramadol can cause less sedation and respiratory depression and has less potential for tolerance compared with other opioids, however, it lowers seizure threshold and can precipitate serotonin syndrome when used with SSRIs or TCAs [64]. Although less pain relief in cirrhotic patients is expected due to reduced biotransformation, this has not been observed in clinical trials. In patients with liver cancer the duration of action is longer compared to healthy controls. Authors recommend tramadol 50 mg every 12 hours [65]. Others have recommended 25 mg every 8 hours in liver dysfunction [31]. Tramadol can be used in patients with hepatorenal syndrome considering dosage adjustment and strict side effects surveillance. Start with 50 mg every 12 hours and use extended dosing intervals [66].

Hydrocodone

Hydrocodone belongs to the group of long acting or slow sustained release opioid analgesics. It is a semi-synthetic drug derived from codeine and is used as an analgesic antitussive [23, 67]. Its drug products are available only in oral form or in combination with non-opioid drugs such as acetaminophen. Even though hydrocodone has been available for clinical use in the US for long time. Its metabolism and kinetics are not fully understood. Its main metabolites are noridrocodone (via cytochrome P450 [CYP]3A4) and hydromorphone (through CYP2D6). The hydromorphone is more powerful and binds much more closely to the μ-opioid receptor than hydrocodone, and probably represents the active metabolite of the hydrocodone [68,69]. Hydrocodone dosage titration is limited due to its non-narcotic composition [11]. We do not recommend it in patients with hepatorenal syndrome.

Levorphanol

Is a potent opioid agonist, with a longer half-life compared to other opioids. It is considered step 3 opioid by WHO. It is a mu, delta, kappa, kappa 3 receptor agonist, potent NMDA antagonist and serotonin/norepinephrine reuptake inhibitor. Levorphanol is used in pain refractory to other opioids, pain in the elderly, neuropathic pain, opioid-induced hyperalgesia [70]. Its method of administration is via IV, subcutaneous and oral route with half-life of 11-30 hours when given via parenteral and oral route respectively. The metabolism of Levorphanol occurs through hepatic glucuronidation that produces levorphanol-3-glucornin and is excreted renally. Although it has a short half-life of approximately 11-16 hours, its duration of analgesic action is longer [71]. It begins to produce analgesia in 10-60 min after oral administration lasting for 6-15 hours with its peak plasma concentration reaching in 1 hour [72]. Levorphanol is five times more potent compared to other opioids such as oxycodone and methadone when given orally and parentally. Prommer et al suggested that total daily dosage should be started at 1/15 to 1/12 of daily dosage oral morphine and change the dosages according to patient's response [72]. The recommended dose via IV route is 1 mg with slow infusion, for subcutaneous, 1-2 mg that can be repeated in 6-8 hour as needed and for oral it is 2 mg [72]. Metabolism of Levorphanol occurs via hepatic glucuronidation producing levorphanol-3-glucuronide which is an inactive metabolite. It has been suggested that the dose interval of Levorphanol should be increased in patients with hepatic insufficiency. Levorphanol has high affinity for protein binding and its metabolites are excreted renally, therefore it is advisable to increase the dose interval in patients with compromised kidneys [73]. Like methadone, levorphanol may cause urinary retention due to its anticholinergic adverse effects [72]. It is not current data that supports the levorphanol dosage adjustment in patients with liver and kidney impairment.

Nalbuphine

It is a kappa opioid agonist and mu antagonist. It produces analgesic effects by its actions on kappa receptors [74]. Nalbuphine is one of the opioids that provides pain control with less nausea, itching, and respiratory depression. It is administered through subcutaneous, IV and IM routes, with rapid onset of action within 15 minutes. Metabolized through hepatic and renally eliminated. Recommended dose of Nalbuphine is 10 mg for 70 kg weight. Patients receiving Nalbuphine can experience certain side effects such as depression, confusion, faintness, changes in vitals, cramps and respiratory depression, dyspnea [75]. Nalbuphine is metabolized and eliminated by the liver and therefore its dose should be reduced in patients with hepatic dysfunction [76]. However, there is insufficient data to recommend this medication to patients with hepatorenal syndrome.

Tapentadol

Dual-acting analgesic molecules such as tapentadol have been used due to the mechanistic mode of action on the mu-opioid receptor (MOR) agonism and noradrenaline reuptake inhibition receptor (NRI). The drug has been increasingly used to treat moderate to severe acute pain, neuropathic progression, and chronic pain [77-79]. Tapentadol is majorly metabolized through conjugation into inactive metabolites, tapentadol-O-glucuronide (55%) and tapentadol sulfate (15%). In addition, liver enzymes CYP2C9 & CYP2C19, and CYP2D6 metabolizes tapentadol (to a lesser degree) producing N-desmethyl tapentadol and hydroxyl tapentadol, respectively; before undergoing further conjugation. In addition, these metabolites have no analgesic effects [22]. First-order kinetics is the channel tapentadol follows during elimination. The kidneys exclusively excrete the drug and its metabolites, 69% is excreted in the form of conjugates, 27% as other metabolites, and 3% as unchanged drug. The half-life of oral tapentadol is approximately 4 hours, and clearance is 1530±177ml/min, but research shows that these rates can be prolonged following dialysis and impaired liver function [78,79]. Tapentadol formulation is in oral tablets, doses consisting of 50, 75 and 100 mg. The recommendable dosage for tapentadol is 75 mg twice daily to a maximum of 650 mg every 4-6 hours. In the context of patients with acute renal impairment or severe chronic hepatic impairment, tapentadol should not be prescribed. Moreover, in aged patients, especially those with moderate hepatic impairment, the dose is reduced [22,46]. Tapentadol should be used with caution since both hepatic and renal functions are impaired during hepatorenal syndrome, there is no data of its usage in this population. Instead, the drug is safe for use in patients showing mild liver disease, but with caution in moderate chronic liver disease, starting with lower doses [46].

Aspirin

Aspirin irreversibly acetylates COX enzymes. COX-2 is an important enzyme responsible for producing renal prostaglandins in charge of the augmentation of renal blood flow (RBF) and GFR (glomerular filtration rate) in situations of decreased actual or effective circulating volume. The main prostaglandins in the kidney are prostacyclin PGI2, PGE2, and PGF2α, which have a complex role. In a healthy population, COX inhibitors have negligible effects on renal hemodynamics. However, volume-depleted states activate RAAS, and consequently, prostaglandins synthesis is increased to preserve RBF by decreasing preglomerular resistance. ASA-induced inhibition of prostaglandins-mediated vasodilation decreases the GFR significantly, increasing the risk for nephrotoxicity, AKI (Acute renal injury), hyperkalemia, renal tubular acidosis. In patients with CKD, RAAS persistent activation produces glomerular capillary hypertension, glomerular damage, extracellular matrix accumulation, reactive oxygen species, and endothelial dysfunction. Higher levels of prostaglandins are present in CKD to attenuate the RAAS effects and to aid in the perfusion of the remaining nephrons by afferent arteriole vasodilation. Thus, in the presence of ASA, these protective mechanisms are shunted, worsening kidney impairment [80, 81, 38]. There is limited data on ASA usage in this population. In general, salicylates should be avoided in patients with AKI due to the increased risk for hypervolemia and systemic vasoconstriction. If salicylates are used, this should be done cautiously and under special circumstances [80, 81, 38]. Salicylates are hepatotoxic in these patients since these drugs are mostly bio transformed through conjugation and CYP450 reactions, which increases its oral bioavailability and plasma levels. There is a 2-fold increase in AUC (Area Under the Curve) of free salicylate, indicating an increased risk of salicylate toxicity in these patients [31]. ASA inhibits prostaglandins production in the kidneys and GI tract, worsening RAAS effects involving sodium retention, ascites, edema. Patients are more susceptible to gastrointestinal bleeding due to decreased cytoprotective effect of COX-1 and thrombocytopenia caused by decreased synthesis of Thromboxane A2 [11, 31, 66, 82, 83]. Salicylates are known to cause prerenal AKI and ATI (acute tubular injury) in patients with deteriorating kidney function. The prostaglandin-inhibitory effect harshly decreases the renal blood flow worsening the already low glomerular perfusion. Salicylates are nephrotoxic drugs that cause tubule-interstitial kidney damage. Besides the nephrotoxic effects, Salicylates are hepatotoxic. ASA can't be metabolized by the liver, increasing its concentration to toxic levels. It is recommended to avoid NSAIDs in hepatorenal syndrome due to toxic effects in both liver and kidney in a population that already has deteriorating functions in these 2 key organs [84, 85].

Non-steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs (NSAIDs) produce their analgesic effect by blocking cyclooxygenase, leading to inhibition of PGE2 and PGI2 production, which are responsible for mediating central and nociceptive responses [86]. The majority of NSAIDs undergo hepatic biotransformation and renal excretion as the primary routes of metabolism and elimination, respectively. Many NSAIDs are metabolized by the liver into inactive metabolites [87]. NSAIDs undergo hepatic transformation via various CYP450 enzymes, mainly CYP2C and CYP3A [86-89]. Most of them also undergo glucuronidation in the liver [89]. Patients with cirrhosis may have decreased production of drug-binding proteins and may have normal or reduced CYZ activity. This results in alteration of the metabolism and bioavailability of NSAIDs in this subset of patients [11,89]. Furthermore, as most NSAIDs are highly protein-bound, the level of free NSAID plasma concentration in patients with cirrhosis is increased, requiring dose reduction [89]. An important adverse effect of NSAID use is hepatotoxicity. This is particularly important due to their widespread use, NSAIDs are responsible for approximately 10% of all cases of drug-induced hepatotoxicity. NSAID use is also a common cause of GI bleeding. In the context of patients with cirrhosis and portal hypertension, there is a significant correlation between NSAID use and the first variceal bleed, as demonstrated in a retrospective case study [36,89]. Due to the diminished synthesis of pro-aggregatory thromboxane A2 by platelets, these patients are also at increased risk of thrombocytopenia and coagulopathy [36]. The greater concern with NSAID use in cirrhotic patients with portal hypertension is the association of renal impairment, in particular hepatorenal syndrome. In cirrhosis, prostaglandins are required to counteract the reduction of perfusion to the kidneys due to the activation of the renin-angiotensin-aldosterone system and sympathetic system. NSAID mediated inhibition of prostaglandins in these patients, which can lead to profound reduction in renal perfusion, reduced GFR, and marked sodium retention [90].

As a class, NSAIDs (including selective cox-2 inhibitors, the coxibs) have an inhibitory effect on the prostaglandins that play a crucial role in maintaining renal perfusion and filtration. This results in hypertension (or worsening of pre-existing hypertension), fluid retention, and acute renal failure in severe cases. Factors that tend to exacerbate this effect are dehydration and pre-existing kidney dysfunction [88]. Afferent artery vasoconstriction leads to a reduction in GFR. Other renal adverse effects of NSAIDs include allergic reactions that can lead to tubulointerstitial nephritis, nephrotic syndromes- most commonly minimal change disease and membranous nephropathy, papillary necrosis, and several electrolyte abnormalities including hyponatremia, hyperkalemia, and type 4 renal tubular acidosis [38]. The use of NSAIDs and selective cox-2 inhibitors should be avoided in the presence of acute kidney injury.

Topical NSAIDs can provide adequate analgesia for both acute and chronic pain with limited systemic exposure as compared to oral NSAIDs, thereby minimizing the systemic toxicities and related adverse effects [38, 90, 91]. When pain is present in non-ulcerated soft tissues and joints, topical NSAIDs may be a suitable alternative to oral administration [38, 91]. Topical NSAIDs include diclofenac, ibuprofen, ketoprofen, and combination salicylates plus diethyl ether [38].

Although serum concentrations of topical NSAIDs are lower than that of oral NSAIDs, they must still be used over small surface areas and not for prolonged durations to avoid systemic toxicity. There is a lack of evidence comparing topical and oral NSAIDs in terms of renal adverse effect profiles [91]. We do not recommend the use of NSAIDs in patient with hepatorenal syndrome

Ketamine

N-methyl-D-aspartate (NMDA) receptor antagonists like ketamine have been used noncompetitively to inhibit these receptors in the brain. Ketamine is a phencyclidine derivative, consisting of a mixture of (S)- Ketamine and (R)-Ketamine, being (S) isomer more potent. Ketamine has different clinical uses, anesthetic, analgesic (chronic and acute postoperative pain), antidepressant, and anti-inflammatory effects. This arylcyclohexylamine anesthetic has been increasingly used during short-term diagnostic and surgical procedures. Ketamine provides a similar analgesic effect as opioids but with mild respiratory depression [92]. Indeed, it has been used as a third-line drug in patients with opioid-resistant pain in palliative care and for chronic noncancer pain [93]. The liver primarily metabolizes ketamine into norketamine (active metabolite), mediated by the cytochrome p450 enzymes CYP2B6 and CYP3A4. It is metabolized via nitrogen demethylation with CYP3A4 majorly demethylating (S)-ketamine enantiomer, whereas CYP2B6 demethylates with equal efficacy both enantiomers, (S)- ketamine and (R)-Ketamine [92]. Norketamine undergoes hydroxylation to produce hydroxynorketamines and dehydronorketamine metabolites. The drug metabolites are subject to passive uptake into the brain to exert the anesthetic effect [92-94]. The kidneys primarily eliminate the drug in levels; 2% ketamine, 2% norketamine, and 16% dehydronorketamine. The 80% of the drug is eliminated via urine and bile as glucuronic acid-labile conjugates (hydroxynorketamines and dehydronorketamines) [92,93].

This study conducted with rats, the aim was to investigate the long-term and high dose administration of ketamine and the histological changes in the liver, they observe structural changes in the mitochondria and endoplasmic reticulum, concluding prolonged and high doses of ketamine cause hepatocellular toxicity and histological changes in the hepatocytes [95]. Some animal studies have shown Ketamine is related to liver damage and cystitis [96]. In humans, the incidence of hepatotoxicity and cystitis may be increased with higher doses and repeated exposure [97]. We do not recommend the use of ketamine in patients with hepatorenal syndrome.

Gabapentin

Gabapentin, a structural analog of GABA, is an approved drug for neuropathic pain management in postherpetic neuralgia (PHN) [98,99]. Initially approved as an anti-epileptic drug, it has been found useful as an off-label drug in other neuropathic pain conditions and several other indications like fibromyalgia, restless leg syndrome, social anxiety disorder and vasomotor symptoms associated with menopause [98,99]. Its mechanism of action involves binding to voltage gated calcium channels in presynaptic membrane and modulation of excitatory and inhibitory neurotransmitter involved in nociception making it an effective pain management option [100]. Gabapentin is administered orally and is available in capsule, tablet or solution form. The extended-release preparations are administered with meals as food delays the absorptions in extended-release preparations thus helping the drug being absorbed more slowly and providing longer duration of action [98,101]. The immediate release preparations can be used without regards to meals as there is no interaction with absorption in this type of preparations. Since it is a GABA analog, it has the same transporter receptors and its absorption is rapid, dose dependent and saturable. Its absorption follows zero order kinetics and it is non-linear [101].

Gabapentin achieves peak concentration in plasma within 2 to 4 hours with immediate release preparations while the extended-release preparations are absorbed more slowly and takes about 8 hours to achieve peak concentration [101]. It is sparsely protein bound with rate as low as <3% and achieves volume of distribution 0.5 to 0.8. L per kg and has a high CSF concentration in the range of 20% of plasma concentration. It is not metabolized by liver or kidney. It does not interact with any enzymes so does not alter metabolism of other drugs and it is excreted unchanged by kidney in the urine [101]. Gabapentin is not hepatically metabolized making it a good option to use for pain management in patients with hepatic impairment. Since it is renally excreted, the half-life varies according to renal function [98]. As a renally cleared drug, the dosage needs to be adjusted in renal impairment [98].

The initial dosage should be titrated as tolerated and effective in individual cases following adult dosage guidelines. Once initial titration is achieved, it should be adjusted as per CrCl measured by Cockcroft-Gault formula [98]. For Extended-release preparations in patient with hepatorenal syndrome, gabapentin is not recommended. For Immediate-release preparations: Maintenance dose adjustment based on creatinine clearance [98].

CrCl (mL/minute)	Dose Adjustment	Maximum daily dose
30 to 49	Reduce by 50%	900 mg in 2 to 3 divided doses
15 to 29	Reduce by 75%	600 mg in 1 to 2 divided doses
<15	Reduce by 90%	300 mg in a single dose

The most concerning side effects of gabapentin are its CNS and respiratory depressant effects [98]. Hepatorenal syndrome (HRS) patients already have altered mental status due to uremia and gabapentin can potentially enhance CNS depression.

Gabapentin, with no hepatic metabolism and enzyme inducing or inhibiting properties of it is a very suitable candidate for pain management in HRS. The dosage adjustment needed in renal impairment needs to be better studied and established. Extended-release preparations are not useful for patients on dialysis, but immediate release preparations can be used and are better suited considering they achieve high plasma concentration more quickly. The CNS and respiratory depressive side effects though can be limiting factors and should be studied further before making it a first line drug. The pain-relieving effects can take up to a week to provide comfort to patients, making it a less favorable option for acute pain management. However, a few cases have reported pain relief in a couple of days and should be studied further.

Pregabalin

Pregabalin, another structural analog of GABA like gabapentin, is an approved drug for pain management in various acute and chronic conditions like neuropathic pain, perioperative analgesia and postherpetic neuralgia (PHN) [102,103]. It also useful in fibromyalgia. Its mechanism of action is similar to Gabapentin and involves binding to voltage gated calcium channels in presynaptic membrane and modulation of excitatory and inhibitory neurotransmitter involved in nociception making it an effective pain management option [104]. However, pregabalin differs in pharmacodynamic and pharmacokinetic properties from gabapentin and it is considered to have better bioavailability and more consistent plasma concentration level providing potentially superior therapeutic effect compared to gabapentin [101]. Pregabalin is administered orally and is available in capsule, solution or extended-release solution forms. The extended-release and immediate release preparations are administered with food to increase bioavailability [102]. Pregabalin achieves peak concentration in plasma under one and a half hours [101]. It follows first order kinetics in absorption. It is not protein bound and achieves volume of distribution 0.5 L per kg. It is not metabolized by liver or kidney and excreted 90% unchanged by kidney [101,102]. Since it is not hepatically or renally metabolized, pregabalin is a good option to use for pain management in patients with hepatic impairment and renal impairment. Since it is renally excreted, the half-life varies according to renal function and its dose needs adjustments in renal impairment.

The initial dosage should be titrated as tolerated and effective in individual cases following adult dosage guidelines. The current guidelines recommend dosage based on GFR (ml/min) as below [22].

- If GFR is <15 ml/min then it should be started at 25 mg daily in divided doses and then titrated as tolerated and needed.
- If GFR is 15-30 ml/min then the initial dose can be up to 50 mg daily in divided doses and then titrated as tolerated and needed.
- If GFR is 30 - 60 ml/min then the dose should be initiated at 75 mg daily in divided doses and titrated as tolerated and needed.

The most concerning side effects of pregabalin is development of angioedema and it warrants prompt discontinuation of the drug [102]. Another potential adverse effect is development of ascites which can be concerning in Hepatic dysfunction, but its rate is <1% and its risk should be assessed in individual cases [102]. There are some cases of hepatotoxicity reported with pregabalin, but it needs more research [105].

Pregabalin, with no hepatic metabolism and enzyme inducing or inhibiting properties of it, is a very suitable candidate for pain management in HRS. It needs dosage adjustment in renal impairment. It is superior to many drugs as it achieves good plasma concentration quickly after oral administration. The hepatotoxic potential should be studied further to determine if it is an actual threat, in which case it will contradict its use in pain management in HRS. The pain-relieving effects can take up to a week to provide comfort to patients, making it a less favorable option for acute pain management.

Acetaminophen

Acetaminophen is the active metabolite of phenacetin. It is a centrally acting cyclooxygenase inhibitor. The activation of descending serotonergic inhibitory pathways in the CNS is believed to cause analgesic effect [106]. The liver plays a major role in paracetamol metabolism. Paracetamol is metabolized to non-toxic metabolites via sulfation and glucuronidation. Only a small portion is metabolized by CYP2E1 producing N- acetyl-p-benzoquinone imine, which is a hepatotoxic substance. This toxic substance conjugates with glutathione and becomes non-toxic cysteine and mercapturic acid conjugates [89]. In patients with chronic liver disease, the half-life of paracetamol may increase. However, CYP450 content is not increased and there is sufficient glutathione to avoid hepatotoxicity. The current recommendation suggests low dose therapy (2-3 g/ day) is well tolerated in patients with liver cirrhosis. However, up to 4g/day is well tolerated by most cirrhotic patients in short-term, including those that consume regular alcohol [89]. Paracetamol overdoses cause hepatotoxicity. It occurs due to formation of N-acetyl-p- benzoquinone imine that binds with hepatocytes causing tissue necrosis. This step is protected by endogenous glutathione unless there is depletion of tissue glutathione. Chronic liver disease patients are also at increased risk for hepatotoxicity, as paracetamol metabolism is decreased in patients with cirrhotic livers [107].

Acetaminophen is preferred non opioid analgesia in CKD who have nociceptive pain. It is extensively metabolized in the liver and only 2-5% of the therapeutic dose is excreted unchanged in the urine. Decreased GFR does not impact acetaminophen elimination [108]. It is recommended to limit daily doses to the above figure of 40mg/kg/day [16].

Some studies have shown that patients with alcoholic or non-alcoholic liver disease have lower levels of glutathione [109,110]. However, in a review of the literature, Lauterburg stated that except for findings in chronic alcoholic patients, no evidence exists of a higher risk for adverse effects from paracetamol in patients in which low glutathione has been observed, for example, patients with chronic hepatitis C or non-alcoholic cirrhosis [111].

IV formulation is contraindicated in patients with severe hepatic impairment or severe active liver disease. It is best to avoid acetaminophen in patients with advanced chronic liver disease or cirrhosis who are actively drinking alcohol, malnourished, or receiving concomitant interacting medication. Some experts would limit the maximum dosage to less than or equal to 2g/day. However, low dose therapy (2 to 3g/day) is usually well tolerated in patients with chronic liver disease or cirrhosis in absence of other factors increasing the risk of acetaminophen-induced hepatotoxicity [106].

Recent reviews have concluded that paracetamol is a safe and effective first line agent in almost all patients regardless of liver disease etiology. Although the need for dose reduction in the healthy population seems largely unnecessary, it may be warranted in certain severe or decompensated hepatic disease states, particularly if patients are malnourished, are not eating or have a dry weight less than 50 kg. The prescribers should be encouraged to consider appropriate dosing for each individual patient, considering their underlying disease state and the pharmacological covariates [112].

Acetaminophen is safe to use in kidney disease. Recent reviews suggest acetaminophen is safe and effective first line analgesic in almost all patients regardless of liver disease etiology. However, dose adjustment is warranted for some patients in certain severe or decompensated hepatic disease, particularly if patients are malnourished or have a dry weight of less than 50Kg [112].

Neuropathic pain

Cannabis

The cannabis plant contains numerous phytocannabinoids, the most abundant being delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), cannabivarin, and cannabigerol [113]. Medical use of cannabis was authorized by 31 states of the USA, the District of Columbia, Guam and Puerto Rico, but not all programs are operational [114]. Cannabis formulations have been used medically to treat childhood epilepsy, especially refractory seizures, but its use in the management of pain has still been a controversial debate. A cannabis formulation containing equal proportions of THC and CBD has been medically approved to treat pain and muscle spasticity due to multiple sclerosis in Canada and 26 other countries. Still, it has been prohibited from use in the United States of America [113]. Pain receptors are located throughout the body, and the different pain sensations perceived by these receptors travel to the brain from peripheral nerves through 3 main pathways. In experimental animals, Cannabinoids have shown positive results in blocking the pain sensations of the peripheral nerves, as there are abundant receptors for cannabinoids in the peripheral nerves. However, due to ethical and logistical barriers to conducting similar experiments on human volunteers, marijuana's efficacy in neuropathic pain management is yet to be conclusively confirmed [115]. The most common methods of consumption of cannabis (medical or recreational) are smoking, inhaled vapors and oral routes of administration. Due to the poor solubility in water, intravenous administration of THC is very rarely used [116]. Transdermal routes for medical and cosmetic purposes have shown no scientific evidence of any systemic pharmacologic activity [117]. Rapid absorption is achieved when consumed via smoking or inhaled vapors, with THC levels in plasma being detectable within seconds. It, therefore, results in rapid onset of action compared to the oral route (slowest onset of action) and causes more intense effects [118].

Metabolism of THC primarily occurs by the hepatic cytochrome P-450 isozymes 3A4 and 2C9 and is excreted mainly in feces (65-80%) and urine (20-35%). Due to the extensive storage of THC in the fatty tissues and subsequently slow release into the circulation, the drug test for THC and metabolites in urine and blood may test positive for several weeks after the last cannabis intake in chronic users [119-121]. Acute hepatotoxicity has not been associated with cannabis use [122]. Although its use in patients with moderate to severe hepatic impairment is not recommended, it is advised to use it with caution in patients with mild hepatic impairment. The impact of cannabis use on patients with kidney dysfunction is yet to be studied conclusively. THC, being a substrate for the CYP2C9 and CYP3A4 drug-metabolizing enzymes, has potential drug interactions with other medications [119,123]. We do not recommend its use in patients with hepatorenal syndrome.

Duloxetine

Duloxetine is part of the serotonin norepinephrine reuptake inhibitors family which are widely used antidepressants [124] as well as for diabetic neuropathy, it has not only been used for psychiatric conditions but also has been used for various pain conditions. Duloxetine has a three-ring chemical structure. Duloxetine has successfully been used in patients who suffer from CKD and ESRD [125]. Those patients who suffer from kidney disease have shown to have a decrease in clearance of duloxetine so therefore it is recommended that patients with CKD and ESRD reduce their dose by 50% [125]. The route of administration for duloxetine is oral due to better absorption in the gut. The half-life of duloxetine varies from person to person and has been reported to be 10-12 hours [124]. The bioavailability once ingested is around 50% [126]. It is metabolized by liver enzymes specifically P-450 isoenzymes. Studies have reported the time to peak plasma concentration which does vary when it comes to fed 10 hours, unfed; about 6 hours. The drug is cleared via hepatic and renal clearance however it is strongly advised against anyone with hepatic disease of any sort. However, those with kidney disease are able to tolerate it but the dose must be adjusted. The patients with kidney disease and GFR < 30 ml/min are not recommended to take duloxetine. Liver test abnormalities with ALT elevations above 3 times the upper limit of normal have been reported to occur in ~1% of patients on duloxetine, but elevations were usually self-limited and did not require dose modification or discontinuation. Rare instances of acute, clinically apparent episodes of liver injury with marked liver enzyme elevations with or without jaundice have been reported in patients on duloxetine. The onset of injury is usually within 1 to 6 months and the pattern of serum enzyme elevations is usually hepatocellular, but mixed and cholestatic forms have also been described [105].

Venlafaxine

Serotonin-norepinephrine reuptake inhibitors (SNRIs) like venlafaxine have been increasingly used for the treatment of neuropathic pain [31]. It is primarily metabolized by the liver into several inactive and one active metabolite mediated by CYP2D6 and to a lesser extent by CYP3A4 [31]. It is metabolized through O-demethylation via CYP2D6 into its active metabolite O-desmethylvenlafaxine [127,128]. This subjects it to drug - drug interactions with CYP2D6 inhibitors/inducers and pharmacogenomic variability. Less than 5% of venlafaxine and about 30% of O-desmethylvenlafaxine are excreted renally [128]. Despite this, the half-life of both venlafaxine and O-desmethylvenlafaxine has shown to be significantly prolonged in those with renal impairment and in those receiving dialysis [128]. Desvenlafaxine, the commercially available O-desmethyldesvenlafaxine metabolite, is about 45% excreted unchanged in the urine and about 55% metabolized through phase II glucuronidation via UDP-glucuronosyltransferase enzymes [129,130]. This has also shown to have a prolonged half-life in those with renal impairment [129,131]. The usual recommended dose of venlafaxine for managing neuropathic pain is 37.5mg once or twice daily to a maximum of 225mg/day [127]. However, in the setting of renal impairment (GFR of 10-30mL/min), the dose should be reduced by 50%2. Similarly, in the setting of moderate hepatic impairment, the dose should be reduced by 50% [127]. This is because, in patients with moderate hepatic impairment, significant alterations were observed in the t1/2 (30% and 60% prolongation) and clearance (50% and 30% decrease) of venlafaxine and its active metabolite, respectively [31]. In patients with severe hepatic impairment, a decrease of up to 90% was observed in venlafaxine clearance [31]. Since both hepatic and renal functions are significantly impaired in hepatorenal syndrome, a reduced dose of venlafaxine can be both potentially safe and beneficial in managing pain in these patients. Additionally, careful drug monitoring is required if this drug is prescribed concomitantly with an SSRI to prevent drug-drug interaction leading to serotonin syndrome.

Fluoxetine

Selective serotonin reuptake inhibitors (SSRIs) like fluoxetine have long been debated to have therapeutic potential for neuropathic pain. The exact mechanism of action of SSRIs in neuropathic pain management is unknown but researchers believe that it may be related in part to the presynaptic inhibition of the reuptake of serotonin and norepinephrine in pain inhibitory pathways, as well as peripheral mechanisms involving beta 2 adrenergic receptors and the opioid system [132,133]. The pharmacological advantages of SSRIs result from this high selectivity for the serotonin receptor and the low or null affinity for all other types of receptors [134]. SSRIs increase synaptic serotonin by blocking the neuronal transport of it, which then leads to a stimulation of postsynaptic serotonin (5-HT) receptors such as 5-HT1B, 5-HT1D, 5-HT3 and 5-HT2C [135]. Stimulation of different receptors leads to its analgesic effects [136]. Additionally, there is some evidence that the effect is also mediated through inhibition of noradrenaline rather than serotonergic reuptake [137]. Furthermore, facilitatory actions of serotonin on 5HT3 receptors subserves pronociceptive function and therefore enhances pain [138,139]. Thus, SSRIs predictably result in poorer pain control. Smith et al. analyzed the existing literature to evaluate the efficacy of SSRIs in the treatment of chronic pain however, the results were conflicting [140]. Similarly, a trial conducted on 46 patients on fluoxetine revealed improvement of fibromyalgia pain [141] but no apparent effect on diabetic nerve pain [142].

Another trial conducted on 98 patients with idiopathic facial pain found that fluoxetine was more effective than placebo [143]. A randomized, double-blind study comparing the efficacy of fluoxetine to other antidepressant in patients with postherpetic neuralgia showed that clinically meaningful pain relief (moderate or better) was least with fluoxetine (5/15 patients) as compared with the other antidepressants [144]. Overall, there is some evidence for the effectiveness of fluoxetine in fibromyalgia, although a higher-than-normal dose may be required [135]. Fluoxetine is extensively metabolized in the liver by demethylation which is carried out by the enzyme CYP2D6 to its primary active metabolite norfluoxetine (desmethyl fluoxetine) [22]. About 60% of the drug and its active metabolite are excreted renally and therefore, patients on chronic treatment with severe renal failure should be monitored carefully. The usual recommended dose of fluoxetine is 20-60 mg depending on the indication [22]. However, in the setting of renal impairment (GFR < 10 mL/min), a lower dose or less frequent dose should be used which can be subsequently increased according to the response [22]. This is because the elimination half-life of both fluoxetine and norfluoxetine is 4-6 days [22]. Lastly, fluoxetine can increase the risk of gastrointestinal bleeding from varices in patients with hepatic impairment and thus are not the first-choice treatment for neuropathic pain in such patients [145]. Thus, the burden lies on the treating physician to determine if the risks outweigh the benefits in starting a patient with hepatorenal syndrome on fluoxetine for pain control.

Paroxetine

It belongs to SSRIs- Selective Serotonin Reuptake Inhibitors group of drugs. It shows psychiatric effects due to an increase in the serotonin levels in the brain by blocking the serotonin reuptake at the synaptic cleft in the CNS [146]. Amongst the SSRIs class of drugs as well as all other antidepressants which are currently available, paroxetine is considered the most potent serotonin reuptake inhibitor [146]. The liver is the site for extensive metabolism to inactive metabolites for paroxetine. The elimination of the metabolites is via urine (64% of the dose) and feces (36% of the dose), which shows that it is eliminated by metabolism [22]. So, a longer half-life is seen in patients with hepatic impairment as compared to healthy subjects. Therefore, in these patients, the drug concentration in plasma will be extremely higher compared to healthy patients at a particular dose [147]. There were no significant changes in the laboratory tests of liver function by paroxetine administration up to 14 days (2 weeks) of drug initiation in patients with hepatic dysfunction or in healthy patients. Thus, in patients with hepatic dysfunction, paroxetine is safe to use if the dose used is lower in the dose range recommended for healthy patients without liver dysfunction [147]. Episodes of liver injury could occur with onset usually within 2-16 weeks or up to 1 year. It is not required to change the doses or stop the paroxetine therapy, because the elevation in serum aminotransferases levels that could occur is usually self-limited. Chances of acute liver failure or chronic liver injury are very rare [105]. Considering potential risk of accumulation, we do not advise its use in patients with hepatorenal syndrome.

Valproic acid

The metabolism of Valproic acid is impaired in hepatic disease. Decreased metabolism tends to increase the total serum level of valproic acid. The hepatic enzyme, CYP3A4, is affected in hepatocellular dysfunction, therefore, it is important to know the inductor/inhibitor profile of valproic acid [148]. Valproic acid is a wide-spectrum isoenzyme inhibitor that can increase its plasma concentration along with other drugs, causing toxicity. It has idiosyncratic effects which can lead to hepatotoxicity and Rey's syndrome [148]. Valproate should be avoided in patients with known liver pathology [149]. In case of liver failure, protein binding capacity is lowered without changing hepatic intrinsic clearance, the total concentration of the drug will fall because the metabolism depends on the free fraction [148]. Conversely, drug concentration increases when intrinsic clearance is reduced which causes toxicity. [148]

Carbamazepine

Carbamazepine is a lipophilic drug, metabolized in the liver to active metabolites including carbamazepine-10 and 11-epoxide [22]. It is used for diabetic neuropathy. There have been reported cases of hepatotoxicity with carbamazepine, we do not recommend the medication in patients with hepatorenal syndrome.

Nortriptyline, amitriptyline, desipramine and clomipramine

These tricyclic antidepressants have been involved in liver damage and elevation of aminotransferases. These drugs have been commonly used for the treatment of depression, belongs to secondary amines tricyclic antidepressants which block serotonin and norepinephrine reuptake at synaptic cleft, but more potently blocks norepinephrine reuptake [150,151].

Off-label use of it has been seen in the management of neuropathic pain, irritable bowel syndrome, bulimia nervosa, overactive bladder, post-herpetic neuralgia, and ADHD [152]. In patients with diabetic neuropathy, cautious use of TCA drugs (desipramine, amitriptyline, nortriptyline) can be done for the management of neuropathic pain due to its higher risk of side effects [153]. It is extensively metabolized in the liver, predominantly by the CYP2D6 enzyme, thus producing toxic intermediates due to metabolism which could cause liver injury [105]. For this reason, it is not recommended in patients with hepatorenal syndrome.

Topical Lidocaine

Lidocaine is an amide-type local anesthetic with faster, longer-lasting effects; it is also a Class 1b antiarrhythmic agent used to depress ventricular arrhythmia. Moreover, it has antinociceptive, immune-modulating, and anti-inflammatory properties [154]. Lidocaine's primary mechanism of action is through blockade of voltage-gated sodium channels (VGSCs) inhibiting action potentials generation in peripheral neurons [155]. Its absorption depends on the duration of application, dosage, route of administration, and surface area. It is rapidly absorbed after IV administration, and if a local anesthetic is applied on mucosal surfaces (tracheobronchial tree). When given IV, the volume of distribution is 0.6-4.5 L/kg [154]. Lidocaine is approximately 60-80% bound to plasma protein alpha 1 acid glycoprotein; this glycoprotein is increased in the presence of conditions such as cancer, surgery, trauma, myocardial infarction, smoking, and uremia; and decreased with the use of oral contraceptives. Lidocaine can diffuse lipophilic cell membranes in its uncharged (free) base form. It crosses the placenta and brain blood barrier by passive diffusion [22,156]. Lidocaine is metabolized rapidly by the cytochrome P450 system in the liver into monoethylglycinexylidide (MEGX) and glycinexylidide (GX), these are similar to lidocaine but less potent. Both key metabolites have longer half-lives than lidocaine and mostly contribute to the therapeutic and toxic effects of lidocaine. In conditions with decreased hepatic blood flow (such as congestive cardiac failure, chronic liver disease, hepatic insufficiency, and after acute myocardial infarction) the metabolism of lidocaine is reduced. Lidocaine and its metabolites are mainly renally excreted, only <10% of lidocaine is excreted unchanged in the urine. The primary metabolite in urine is a conjugate of 4-hydroxy-2,6-dimethylaniline. The half-life of lidocaine is around 100 min following IV administration. It follows linear pharmacokinetics [22,154,156]. The maximal safe total dosages for topical lidocaine are 300mg in a healthy 70 kg adult. Its peak anesthetic effect occurs within 2-5 minutes and its effect lasts for 30-45 minutes. Topical lidocaine has different presentations such as creams, patches, gels, and sprays. Lidocaine patches (usual concentration 1.8%-5%) are commonly used for neuropathic pain, these have low (3 to 5%) systemic absorption through the intact skin, not causing toxic blood levels, making it a good option in patients with chronic liver disease and or kidney dysfunction (hepatorenal syndrome). Mild warming of skin enhances the delivery of the drug into the skin. 1 to a maximum of 3 patches should be applied over the painful area for up to 12 consecutive hours in 24 hours, referred to in table *1*. If local anesthetics are applied to mucous membranes or damaged skin this carries systemic toxicity [156-159].

Capsaicin

Capsaicin is an active ingredient in hot chili peppers. It is a transient receptor potential vanilloid 1 (TRPV1) receptor agonist of small peripheral sensory nerves. Capsaicin depolarizes TRPV1 receptors, causing initially a burning sensation due to a transient period of hypersensitivity, and subsequently desensitization of nociceptive areas. Indeed, capsaicin is used for chronic pain from peripheral neuropathy and minor musculoskeletal pain. Other pharmacologic effects capsaicin has shown are its antineoplastic, and cardioprotective effects [160,161]. Capsaicinoids effects depend on the dose and time of exposure. A high dose of capsaicin for a long period causes peptic ulcers, GI cancers and worsens breast cancer. Systemic absorption of topical 8% patch is short, being its plasma concentration low and transient (Cmax of 1.86 ng ml-1 and mean elimination half-life of 1.64 h). Topical capsaicin has a longer elimination half-life compared to oral capsaicin (24.9 min) probably due to slow release from the patch to the skin. Capsaicin is metabolized rapidly (20 minutes) by the liver (CYP enzymes) but its metabolism in the skin is very slow (about 20 hours). In vitro hepatic metabolism, the most abundant metabolite was 16-hydroxycapsaicin, followed by 16,17-dehydrocapsaicin. In the skin, predominant metabolites include vanillylamine and vanillic acid [162,163]. The topical capsaicin presentations with low concentrations (0.025-1%) such as creams, gels, lotions, and patches can be used for daily skin application. The Capsaicin 8% patch (high concentration) follows a defined procedure performed by a health professional due to increased risk from unintended exposure of capsaicin to mucous membranes. Maximum 4 patches can be applied for 30 or 60 minutes for up to 12 weeks. High capsaicin concentration patch main advantages are the long-term pain relief effect, few systemic adverse effects due to poor absorption. Local side effects (erythema, burning sensation) are common but transient. Due to its low systemic plasma concentration, local capsaicin can be used in patients with cirrhosis, hepatorenal syndrome without dose adjustment [159, 160, 163, 164]. In *table 1* we compared lidocaine patches vs capsaicin patches dosage and side effects.

Table 1: Comparison between topical lidocaine and capsaicin patches [157,161].

Drug	Dose	Indication	Side effects and risks	Dose recommendation in hepatorenal syndrome
Topical lidocaine patch (1.8 % or 5%)	1-3 patches applied to intact skin for up to 12 hr/day	Peripheral neuropathic pain	Local side effects: Pain, pruritus, erythema, and skin irritation	No need for dose adjustment
Topical Capsaicin patch (8%)	1-4 patches applied to intact skin by health care profession for 30-60 minutes every 3 months	Peripheral neuropathic pain and minor musculoskeletal pain	Local side effects: Pain, burning sensation, erythema. Transient increased blood pressure	No need for dose adjustment

Source: Comparison between topical lidocaine and capsaicin patches obtained from "Topical lidocaine for neuropathic pain in adults (Review). Cochrane Database of Systematic Reviews" by Derry S, Wiffen PJ, Moore and "Systematic review of topical capsaicin for the treatment of chronic pain" by Mason L, Moore R, Derry S.

Clonidine

Alpha 2 agonists like clonidine act on the central αlpha 2 adrenoreceptors thereby reducing the sympathetic outflow to the body and prolonging pain control [165]. Almost 50% of clonidine is metabolized by the liver of which, 40-60% is excreted unchanged by the kidneys [22]. This warrants a cautious approach to the initiation of clonidine in patients with significant renal dysfunction. Lowenthal et al. recommended individualizing dose according to patient response, as patients with advanced kidney impairment may also have impaired alpha-adrenergic responsiveness [166]. The usual recommended dose of clonidine is 50-100 mcg three times a day, to a maximum of 1.2 mg. It's half-life is 10-20 hrs in patients with normal renal function and 41 hrs in the setting of end stage renal. As such, the plasma concentrations for a given dose of clonidine are 2-3 times higher in patients with severe renal impairment [22]. Despite this, it is interesting to note that even in the setting of renal impairment (GFR < 10 mL/min), a normal dose can be used. No dose adjustments are necessary in the case of hepatic impairment [166]. These attributes make this drug a potential option for pain management in medically challenging situations like hepatorenal syndrome where other commonly available analgesics need to be used with great caution. Additionally, the dose of clonidine can be modestly reduced when it is added to local anesthetics or used as an adjunct to narcotics for pain control [165]. Care should be taken to avoid potentially hazardous drug -drug interactions with antidepressants, beta blockers, cyclosporin, and sympathomimetics. Lastly, a randomized controlled trial (NCT03342950) was conducted to study the effects of topical clonidine and pentoxifylline on patients with neuropathic pain [167]. The outcomes measured were an analysis of pain relief and a change in the visual analogue scale score [167]. Once the results of this trial are made available, more concrete conclusions can be drawn regarding the therapeutic potential of clonidine in neuropathic pain.

Conclusions

Pain management in patients with hepatorenal syndrome poses a unique challenge as most analgesics are metabolized by either the liver or the kidneys. The paucity of evidence-based guidelines for pain management in this patient population often leads to under-treatment. Overall, initiation of drugs at a low dose, careful titration to achieve optimal efficacy with minimal side effects should be the goal. Certain high potency opioids like Sufentanil, Fentanyl, Remifentanil, Oxymorphone, and Butorphanol can be used cautiously. Low potency opioids such as Pentazocine, Tramadol, Nalbuphine, and Tapentadol may also be considered with dose adjustments. Albeit less favorable, but some other analgesic options include Gabapentin, Pregabalin, acetaminophen, Duloxetine, Venlafaxine, Fluoxetine, Topical Lidocaine, Capsaicin, and Clonidine. Further research into the administration of these agents will lead to more efficient and safer pain management in this setting.

Conflict of Interest

The authors declare no conflict of interest.

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