Therapeutic Reviews

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Prescribing in Chronic Severe Hepatic Impairment

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Introduction

The recommendations in this paper are *not* comprehensive, more a direction of travel than a detailed road map. Specific recommendations are limited to common classes and types of drugs used in palliative care. For other drugs, see the relevant *PCF* monograph and the manufacturer's PI. However, some PIs are unnecessarily restrictive.[1]

There will be occasions when hard evidence is not available, and clinicians may have to *prescribe and proceed with caution*, e.g.:

- reduce polypharmacy as much as possible
- avoid hepatotoxic drugs if possible
- use a low starting dose
- reduce frequency of administration
- titrate upwards slowly
- monitor for both early and late onset toxicity (accumulation more likely if the plasma halflife is prolonged)
- ensure that the patient does not become constipated (may cause encephalopathy)
- beware of sedation (may cause, worsen or mask encephalopathy; see Box A).

When deciding drug doses in hepatic impairment, it is important to also take the patient's overall clinical condition and rate of deterioration into account, and *not* rely solely on liver function tests (LFTs); of the latter, tests of synthetic liver function, i.e. albumin and clotting times (e.g. prothrombin time), are considered more helpful and are included in the Child Pugh score (see below).

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Palliative care services are increasingly involved in the care of patients with chronic liver disease, either alone or as a comorbid condition. Because hepatic impairment often changes the pharmacokinetic and/or pharmacodynamic effects of a drug, this presents a challenge for prescribers.

The main aim of this article is to provide guidance for prescribing commonly used drugs for palliative care symptom relief in patients with chronic severe hepatic impairment *and a prognosis of weeks–months or longer*. However, for completeness, a section on last days of life has been included.

Tables have been produced to highlight, when possible, the most, intermediate and least 'hepatically safe' drugs for *chronic use*. However, sometimes the cautious use of a familiar drug may be preferable to an unfamiliar (albeit 'hepatically safer') one. Similarly, we do *not* advocate the automatic switching of patients to a 'hepatically safer' drug when an alternative is proving satisfactory. Finally, this article aims to complement and not replace specialist hepatology guidance.

In palliative care, common liver problems encountered include cholestasis, liver metastases and chronic liver disease, e.g. secondary to alcohol or NAFLD (non-alcoholic fatty liver disease). Symptoms will vary with the underlying cause, but pain, fatigue, sleep disturbance, mood disturbance, pruritis, muscle cramps, anorexia and weight loss are common.

Cholestasis or liver metastases are characterized initially by abnormal LFTs, although synthetic liver function (i.e. albumin, prothrombin time) may be normal.

Chronic liver disease or progressive liver damage leads to fibrosis and subsequently cirrhosis. With severe cirrhosis, liver function is abnormal (decompensated) and the disorganized anatomy results in portal hypertension and complications such as esophageal varices and the risk of major (sometimes fatal) hemorrhage, ascites, hepatic encephalopathy (see Box A) and sepsis.

Patients with portal hypertension are at risk of hepatorenal syndrome. Portal hypertension leads to splanchnic vasodilation and a 'splanchnic steal syndrome' resulting in reduced arterial blood volume. Compensatory mechanisms initially maintain the systemic circulation but, when these fail, it can result in renal vasoconstriction, oliguria, and functional renal insufficiency (hepatorenal syndrome).[2] This carries a prognosis of weeks to a few months (see Simplifying hepatic drugs below).

Box A. Hepatic encephalopathy[3,4]

A neuropsychiatric disorder caused by effects on the CNS of toxins which accumulate in the blood because of inadequate hepatic detoxification.

It manifests as a spectrum of abnormalities affecting cognition, attention, functional ability, personality and intellect, and ranges from mild alteration of cognition ± drowsiness to coma. It is also characterized by neuromuscular symptoms, such as flapping tremor (asterixis), and hyperreflexia.

The time course for hepatic encephalopathy can be episodic, recurrent (<6 months) or persistent (a pattern of behavior changes which are always interspersed with relapses of overt hepatic encephalopathy). It can occur either spontaneously or be precipitated by constipation, sedatives, GI bleeding, dietary protein, uremia, metabolic alkalosis and infections. Most of these result in an increase in blood levels of ammonia, the putative cause of the neuropsychiatric symptoms.

Grade 1
Minimal lack of awareness
Euphoria or anxiety
Shortened attention span
Impaired performance of addition

Grade 2
Lethargy or apathy
Minimal disorientation of time or place
Subtle personality changes
Inappropriate behavior
Impaired performance of subtraction

Grade 3
Somnolence–stupor (but responsive to verbal stimuli)
Confusion
Gross disorientation

Grade 4
Coma (unresponsive to verbal or noxious stimuli)

When prescribing drugs, patients with decompensated liver function require the most caution. Unlike renal impairment, there is no one parameter which indicates the extent to which drug clearance will be affected by hepatic impairment. However, the Child-Pugh score, designed as a *prognostic aid in cirrhosis*, gives a general indication of the degree of hepatic impairment (Table 1).[5]

Table 1
Child-Pugh score: see footnote for interpretation

		Score each factor:		
Factor	Units	1	2	3
Serum bilirubin	micromol/L	<34	34–51	>51
	mg/dL	<2	2–3	>3
Serum albumin	g/L	>35	30–35	<30
	g/dL	>3.5	3–3.5	<3
Prothrombin time (*or* INR)	%	>70	40–70	<40
		<1.7	1.7–2.3	>2.3
Ascites		None	Easily controlled	Poorly controlled
Hepatic encephalopathy (see Box A)	Grade	None	1–2 (subtle changes)	3–4 (drowsy–deep coma)

Assign each factor a score of 1–3 as indicated in the table; total the score and interpret as follows:
Score of 5–6 = Child-Pugh A (well compensated liver function); 1 year survival = 100%
Score of 7–9 = Child-Pugh B (moderate functional impairment); 1 year survival = 80%
Score of 10–15 = Child-Pugh C (severe impairment, hepatic decompensation); 1 year survival = 45%.

The drug literature generally refers to grades of hepatic impairment or to hepatic failure, and not to Child-Pugh scores. Pragmatically, one can regard Child-Pugh categories as roughly equivalent to mild, moderate and severe impairment. *However, it remains important to also take into account the patients overall clinical condition, rate of deterioration and signs/symptoms of decompensated liver function.*

Drug-induced hepatotoxicity

Drug-induced hepatic impairment can be directly hepatocellular or secondary to biliary stasis (bile salts are hepatotoxic), or a combination of both. It is one of the main causes of *acute* liver failure (fulminant hepatic failure), characterized by jaundice, coagulopathy and encephalopathy, and is a medical emergency.

The underlying mechanism varies, but clinically it often resembles viral hepatitis: rapid onset malaise and jaundice with raised plasma aminotransferase concentrations.[6] Raised alkaline phosphatase and bilirubin concentrations predominate in hepatotoxicity secondary to cholestasis.

Hepatotoxic drug reactions can occur in any patient group, but the consequences can be particularly serious in those with pre-existing chronic liver disease. They can be divided into intrinsic (*predictable, dose-dependent*) and idiosyncratic (*unpredictable, dose-independent*). For the intrinsic group, safe dose recommendations are generally informed by early-phase drug studies. Nonetheless, despite usual doses, toxicity may occur in the presence of factors which either increase susceptibility (e.g. hepatic impairment, alcoholism, malnutrition), and/or drug exposure (e.g. drug–drug interaction, genetic variation in CYP450 enzyme activity). Although not completely clear-cut, the following drugs used in palliative care are potential causes of predictable hepatotoxicity:

- acetaminophen (paracetamol), generally with doses >4g/24h *but toxicity has been reported with normal or lower doses in the presence of additional risk factors*[7]
- dantrolene particularly with doses ≥400mg/24h
- fluconazole and itraconazole, particularly if prolonged course and high dose
- rifampin (rifampicin), used to treat cholestatic pruritus[8]
- tizanidine ≥12mg/24h
- valproic acid (valproate), toxicity mostly limited to children <3 years.[9]

LFTs, particularly synthetic liver function in patients with pre-existing hepatic impairment, should be monitored as per the individual PIs.

On the other hand, most drugs at recommended doses can cause idiosyncratic (*dose-independent*) liver injury, with a frequency ranging from 1/1,000−1/100,000 patients, and with a female preponderance of 3:1.[6] Latency ranges from a few days to 6 months, occasionally longer.[10,11] Fatalities have been reported.[10]

Drug-induced mild elevation of liver enzymes is relatively common and, by itself, does *not* necessitate immediate discontinuation of the drug; the situation including synthetic liver function tests should be monitored. The enzymes often spontaneously revert to normal but occasionally increasing concentrations will subsequently necessitate discontinuation.

Drugs used in palliative care most likely to cause idiosyncratic *(dose-independent)* drug-induced liver injury include:[12,13]

- NSAIDs, notably diclofenac (5/100,000 users/year)
- antimicrobials, notably amoxicillin, co-amoxiclav, fluoroquiolones, macrolides, nitrofurantoin
- carbamazepine, valproate
- PPIs.

In patients with hepatic impairment, drugs causing intrinsic *(predictable, dose-dependent)* toxicity do so at lower doses; but there is *not* a uniform increase in the risk of idiosyncratic *(unpredictable, dose-independent)* toxicity.[6]

The use of hepatotoxic drugs in a patient with cirrhosis increases the risk of hepatic encephalopathy (Box A).

PHARMACOLOGICAL IMPACT OF HEPATIC IMPAIRMENT

The liver is the main site for the metabolism of most drugs. However, hepatic reserve is large and, generally, there must be severe hepatic impairment or decompensation for the overall intrinsic activity or capacity of the metabolizing enzymes to be altered to a clinically important extent. However, for drugs metabolized mostly by a specific CYP450 pathway, e.g. sertraline, problems may arise with mild impairment.

However, hepatic impairment can also impact upon the action or overall clearance of a drug in multiple other ways (Box B). In addition, patient-related factors, e.g. disease type/severity and rate of change in LFTs/synthetic liver function, also contribute to the overall pharmacological impact.

Box B. Summary of the impact of hepatic impairment on drug pharmacology

Pharmacokinetic (see also main text below)

Absorption

↓ intestinal bile salts in cholestasis → ↓ absorption of lipid-soluble drugs

Ascites or edematous bowel → ↓ absorption

↓ hepatic blood flow, e.g. cirrhosis, cardiac failure → ↓ first-pass metabolism → ↑ bio-availability, ↑ halflife

Distribution

Ascites → ↑ volume of distribution of water-soluble drugs

Hypo-albuminemia or hyperbilirubinemia → ↑ active unbound drug for highly protein-bound drugs

Metabolism

Accumulation of pro-drugs, drugs and/or metabolites

Active drugs: ↓ enzymatic function (e.g. CYP450) → ↑ effect/risk of toxicity, ↑ halflife

Pro-drugs: ↓ enzymatic function or capacity (e.g. CYP450) → ↓ effect

Elimination

Cholestasis → ↓ elimination of drugs excreted in bile → ↓ enterohepatic circulation

Pharmacodynamic

Altered receptor sensitivity to the effects of drugs

Anticoagulants → ↑ risk of bleeding

Antihypertensives → ↑ risk of hypotension

Benzodiazepines, psychotropics, opioids → ↑ sedation → ↑ encephalopathy

Diuretics → reduced response

Hypoglycemics → ↑ risk of hypoglycemia

NSAIDs → ↑ risk of GI bleeding; fluid retention, ↑ risk of hepatorenal syndrome

Secondary phenomena necessitating extra caution
Ascites: products with a high sodium content and salt and water-retaining drugs, e.g. NSAIDs, corticosteroids
Coagulopathy: anticoagulants, corticosteroids, NSAIDs, SSRIs,
Disruption of the blood-brain barrier → higher CNS concentrations of some drugs, e.g. propranolol
Encephalopathy:
- increased sensitivity to hypnotics and other CNS depressants, including opioids
- diuretics, corticosteroids (if these cause hypokalemia)
- drugs which constipate, e.g. antimuscarinics, opioids (slowed bowel transit time → increased ammonia absorption)

QT prolongation: ↑ risk of ventricular arrythmia with QT prolonging drugs, e.g. citalopram
Renal impairment → ↓ elimination of renally excreted drugs, e.g. aminoglycosides.

Pharmacokinetic considerations
Also see Box B above.

Absorption
Bile salts facilitate the absorption of lipid-soluble drugs, e.g. ibuprofen. Thus, in cholestasis, absorption will be decreased, leading to reduced plasma concentrations and decreased efficacy.[14] Cholestasis will also decrease the absorption of lipid-soluble vitamins A, D, E, and K, and may also affect enterohepatic circulation (see elimination).

First-pass metabolism and systemic bio-availability
In cirrhosis, portosystemic shunts can lead to a decrease in blood flow through the liver. This can reduce first-pass metabolism of PO drugs, thereby *increasing* bio-availability. In severe hepatic impairment, the degree of caution required is related to the drug's usual PO bio-availability (Table 2).

Table 2
Effect of severe hepatic impairment on PO bio-availability[15]

Usual PO bio-availability	Severe hepatic impairment		Examples
	Effect on PO bio-availability	Change to PO dosing regimen	
High >70%	No change	Reduce maintenance dose[a]	Lorazepam, spironolactone
Moderate 40–70%	May increase	Initial doses should be in the low range of normal; reduce the maintenance dose	Amitriptyline, haloperidol, olanzapine
Low[b] <40%	May increase dramatically	Reduce both the initial dose and the maintenance dose	Domperidone (not USA), granisetron, morphine, ondansetron, propranolol, sertraline

[a]to allow for associated decreased hepatic intrinsic metabolism, i.e. clearance; see below
[b]low bio-availability does not necessarily mean high first-pass metabolism; low bio-availability can also relate to poor absorption from the GI tract.

Distribution and protein-binding
With highly protein-bound drugs (>80%), e.g. phenytoin, the proportion of free drug (free fraction) is greater in hypo-albuminemia. Bilirubin binds to plasma proteins, and hyperbilirubinemia can also increase the free fraction of highly protein-bound drugs. Depending on the characteristics of the drug, a greater free fraction means more drug is available for, e.g. distribution, action, elimination.

Water-soluble drugs, e.g. aminoglycoside antibiotics, will distribute into ascites and, in theory, could reduce systemic availability. Larger loading doses could be required but, in practice, this is unlikely to be a problem if the ascites is treated successfully or drained.

Metabolism
The liver typically converts active lipophilic drugs into inactive hydrophilic metabolites for excretion by the kidneys. However, pro-drugs such as codeine, tramadol, and oxcarbazepine are metabolized by the liver into their active forms. Thus, severe hepatic impairment will reduce the efficacy of pro-drugs to a variable extent. Hepatic metabolism includes:

- *phase I (modification) reactions:* particularly oxidation catalysed by CYP450 enzymes in the endoplasmic reticulum
- *phase II (conjugation) reactions:* particularly glucuronidation catalysed by glucuronyl transferases in the endoplasmic reticulum and cytosol.

In severe decompensated hepatic impairment, drugs predominantly metabolized in the liver will accumulate, with a greater likelihood of toxicity. Phase II enzymes are generally less affected than phase I enzymes, which are also affected to different degrees, e.g. CYP1A2, 2C19>2A6, 3A4>2C9, 2E1.[14] For drugs metabolized via CYP450, there is an increased risk of toxicity from a drug–drug interaction with the concurrent use of an inhibitor of the relevant CYP450 enzyme. The effect of concurrent use of an enzyme inducer is likely to be less predictable. In severe hepatic impairment drug interactions may be unpredictable and fluctuate according to liver function. This requires the close monitoring of drugs with narrow therapeutic ranges, e.g. patients receiving warfarin and direct-acting antivirals for hepatitis C.[16]

Impaired hepatic metabolic capacity may well go hand in hand with impaired hepatic synthetic functions, reflected in an elevated prothrombin time/INR and hypo-albuminemia, and also by encephalopathy (see Box A). These can be used as pointers to the need to reduce maintenance doses.

Elimination

In cholestasis, the clearance of drugs with predominant biliary elimination, e.g. digoxin, fusidic acid, morphine, rifampin and many conjugated drug metabolites, will be impaired. Guidelines for dose reduction in cholestasis exist for many antineoplastic drugs but are mostly lacking for other drugs with biliary elimination. Drugs which undergo enterohepatic circulation, e.g. indomethacin, will be affected, but to an unpredictable extent.[14]

The dose of drugs with predominant renal elimination of unchanged drug ± active metabolite(s) may also have to be adjusted in patients with liver disease because of associated hepatorenal syndrome.
Note. Despite impaired renal function, the plasma creatinine concentration may be normal in patients with a reduced muscle mass. Thus, ideally, *creatinine clearance* should be used to determine the dose of drugs with predominant renal elimination in malnourished, cachectic or sarcopenic patients.[7] Even so, the creatinine clearance tends to overestimate glomerular filtration in these circumstances, and the dose may still be too high.

Pharmacodynamic considerations

In severe cirrhosis, the pharmacodynamics of centrally-acting drugs are also altered because of changes in the blood-brain barrier. Further, *moderate–severe hepatic impairment reduces renal clearance*, necessitating a reduction in the dose of renally-excreted drugs.[17] Thus, when hepatic and renal impairment occur concurrently, extra caution is necessary.

Also see Box B above.

APPROACH TO PRESCRIBING IN LIVER DISEASE

Prescribing for a patient with liver disease should be individualised and pragmatic, balancing the risk vs. benefits in the context of overall goals of care. A cautious approach together with regular monitoring is required, particularly as the degree of impairment can fluctuate.

Generally, the safer drugs are those with high PO bio-availability, minimal hepatic metabolism, low–moderate protein-binding, a short halflife, and no sedative, constipating or hepatotoxic effects.

Recommendations for dose adjustment can only be approximate, and cannot replace careful clinical monitoring, including factors such as:

- underlying diagnosis/prognosis
- rate of disease progression
- changes in synthetic liver function/Child-Pugh score
- overall goals of care.

If in doubt, start with a low dose, and titrate slowly to response (Box C).

Box C. 'Red flags' for considering dose reduction in severe hepatic impairment[14,18]

Consider dose reduction if prescribing a drug which normally:

- has low systemic PO bio-availability because of high first-pass hepatic extraction
- is highly protein-bound and the patient has hypo-albuminemia (<3g/dL) ± elevated plasma bilirubin

- is cleared mainly by phase I hepatic metabolism, i.e. CYP1A2, 2C19, 2D6 or 3A4 and has:
  - a narrow therapeutic range *or*
  - a long halflife.

Other factors indicative of severe hepatic impairment and possible need for dose reduction:
- prothrombin time >130% of normal
- platelets <150 x 10^9/L
- bilirubin >5.8mg/dL
- severe cirrhosis (i.e. Child-Pugh C)
- ascites
- hepatic encephalopathy
- hyponatremia
- moderate renal impairment (eGFR <60mL/min/1.73m^2).

Because patients with cirrhosis are prone to renal injury, *nephrotoxic* drugs, e.g. aminoglycosides, should be used with caution. However, this does not mean that essential drugs should be withheld, but that high-risk patients should be closely monitored.[9]

PALLIATIVE CARE DRUGS FOR LONG-TERM USE IN CHRONIC SEVERE HEPATIC IMPAIRMENT

Many drugs used in palliative care, e.g. antimuscarinics, benzodiazepines, opioids, cause CNS depression ± constipation and can either cause, worsen or mask hepatic encephalopathy (see Box A, and individual sections below).

This section provides guidance for prescribing commonly used drugs for palliative care symptom relief in patients with chronic severe hepatic impairment (roughly equivalent to Child Pugh Class C) *and a prognosis of weeks–months or longer.* For:
- acute hepatic impairment, seek specialist advice from a hepatologist
- mild–moderate hepatic impairment, see the *PCF* individual drug monographs for any relevant information
- patients in the last days of life see the separate section below.

Tables 3–10 and the accompanying text were developed to provide user-friendly summaries to guide rational and safe prescribing in patients with chronic severe hepatic impairment, by raising awareness of:
- suitable drugs and their starting doses
- suitable alternatives when patients experience undesirable effects
- the potential risks of using a less hepatically safe drug.

The tables cover the most common symptom relief drug classes, and highlight, when possible, the most, intermediate and least 'hepatically safe' drugs for long-term use. Because it is generally good practice to become experienced in using relatively few drugs well, the list is purposely limited.

The tables should be used in conjunction with the accompanying text which highlights any general considerations for that class of drug and provides a commentary to help inform choice.

As far as possible, specific prescribing advice is given. Even when a drug appears to be 'hepatically safe', because hepatic impairment can have general effects on pharmacokinetics and/or pharmacodynamics, *smaller starting doses, a slower than usual titration and close monitoring of the patient is advisable, particularly in elderly and/or frail patients.* Drugs with a long halflife may reach steady-state only after 1–2 weeks or more of regular use, and undesirable effects may consequently be 'late onset'. Thus, the adage 'start low, go slow' will generally apply to the use of any drug and particularly those with CNS effects.

In addition to the impact of hepatic impairment and familiarity of use, the selection of the most appropriate drug also requires the prescriber to consider any relevant additional factors such as the presence of concurrent symptoms, co-morbidities (e.g. cardiovascular disease, renal impairment), other drugs (e.g. in relation to a drug-drug interaction, QT prolongation) and patient preference.

Sometimes the cautious use of a familiar drug may be preferable to an unfamiliar (albeit 'safer') one. Similarly, *PCF* does *not* advocate the automatic switching of patients to a 'safer' drug when an alternative is proving satisfactory. This section aims to complement and not replace specialist hepatology guidance.

Additional notes on the use of the tables:

- drugs are categorized as 'generally safer', 'use cautiously' and 'avoid if possible' from a *purely hepatic perspective*, according to the risk of accumulation and/or toxicity with long-term use in chronic severe hepatic impairment
- consensus dosing guidelines are presented. These include off-label use and, in some instances, despite a PI contra-indication in this setting. However, it is impractical to highlight all cases of off-label or contra-indicated use because this can vary according to country, brand, indication, formulations, dose, route of administration or patient population. Prescribers should be aware of the implications of off-label use.[7]

Remember: recommendations can only be approximate and cannot replace clinical monitoring.

Analgesics: Non-opioids (Table 3)

Pharmacokinetic changes

About 5–15% of a dose of acetaminophen (paracetamol) is hepatically metabolized to N-acetyl-p-benzoquinoneimine, a highly reactive hepatotoxic metabolite. The halflife of acetaminophen can be nearly doubled in hepatic impairment.[19] Despite this, PO acetaminophen can still be used in severe hepatic impairment *at a reduced dose and provided there are no additional risk factors for toxicity.*[7,20] Although IV acetaminophen is contra-indicated by the manufacturers in severe hepatic impairment, it is used by some liver units, at a maximum dose of 1g IV t.i.d.[21]

The use of NSAIDs in liver disease is associated with a higher risk of undesirable effects, e.g. renal impairment, bleeding from esophageal varices (also see Box A).[22] Most NSAIDs are highly protein-bound and hepatically metabolized. Thus, most PIs for NSAIDs include active liver disease or moderate–severe hepatic impairment as contra-indications. However, particularly in cancer, the potential analgesic benefit may well outweigh the risk.

The pharmacokinetics of diclofenac and ibuprofen appear not to be affected in hepatic impairment;[23] conversely, even mild hepatic impairment significantly affects the pharmacokinetics of celecoxib.[24]

Cholestasis may reduce the elimination of NSAIDs excreted in bile, e.g. indomethacin and may reduce or delay absorption of fat-soluble NSAIDs, e.g. ibuprofen.[14]

Hepatotoxicity is a rare unpredictable effect seen with most NSAIDs, including coxibs. Diclofenac may have the highest risk and ibuprofen the least.[1]

Choice of non-opioid analgesic

In severe hepatic impairment, the cautious use of reduced doses of PO acetaminophen *provided there are no additional risk factors for toxicity*[7] is preferred to an NSAID, which generally should be avoided. Regular review to exclude other risk factors for toxicity, e.g. weight loss, is required.

If the use of an NSAID is unavoidable, ibuprofen is a reasonable choice in cholestatic and non-cholestatic liver disease. A PPI should be given concurrently due to the high GI risk and renal function should be closely monitored.

For adjuvant analgesics, see the relevant tables below.

Table 3

Non-opioid analgesics in severe hepatic impairment. Before use, see introductory and class specific text above

Drug	PO bio-availability (%)	Protein-binding (%)	Halflife in normal liver function (h)	Significant hepatic metabolism	Significant biliary excretion of drug ± active metabolite(s)	Increase in halflife in severe hepatic impairment	Dose and comments
Use cautiously							
Acetaminophen (paracetamol)[a]	<90	20–30	1–4	Yes; hepatotoxic metabolite	No	50–100%	PO/PR[b]: start with 500mg q8h; maximum 1g q8h
Avoid if possible							
NSAIDs							If unavoidable, use ibuprofen PO 200mg t.i.d. (see text)

[a]use only when no additional risk factors for toxicity[7]
[b]IV acetaminophen is contra-indicated by the manufacturers, but is used by some liver units in reduced doses, e.g. 500mg–1g t.i.d. (also see text).

Analgesics: Opioids (Table 4)

Regardless of the pharmacokinetic changes described below, in severe hepatic impairment there is an increased risk of toxicity with *all* opioids because of increased opioid receptor sensitivity and reduced integrity of the blood brain barrier; further, their sedative ± constipating effects can cause, worsen or sometimes mask encephalopathy. A slower than usual titration and close monitoring of the patient is required.

The PIs of most PO opioids include severe hepatic impairment as a contra-indication. SR products should generally be avoided because of the prolonged duration of action if sedation becomes a problem. The exception may be for **morphine** in stable patients (see below).

Routine use of TD patches is not advised because of the long duration of action with effects lasting for ≥20h after removal. In addition, pruritis may affect tolerability.

Pharmacokinetic changes

For most opioids, there is a risk of accumulation in severe hepatic impairment because of either an increase in PO bio-availability (reduced first-pass metabolism) and/or decrease in hepatic metabolism. For opioids significantly metabolized via CYP450 there is an increased risk of toxicity from a drug−drug interaction with the concurrent use of an inhibitor of the relevant CYP450 enzyme.

For pro-drugs such as codeine and tramadol which are activated by hepatic metabolism, there is a decreased production and metabolism of the active metabolite, leading to an unpredictable effect. There is a lack of data on the use of dihydrocodeine (not USA). Accordingly, these opioids should be avoided in both moderate and severe hepatic impairment.

Morphine has a PO bio-availability of 35% (range 15−64), which increases to almost 100% in patients with severe hepatic impairment with cirrhosis.[25] The plasma halflife is also increased, necessitating a decreased dose and frequency of administration of immediate-release products.[25,26] Generally, morphine should be avoided in patients with hepatorenal syndrome because of the additional risk of toxicity from accumulation of morphine-6-glucuronide in severe renal impairment.[7,24] Morphine can cause spasm of the bile duct/sphincter of Oddi and is contra-indicated in biliary colic; this should be considered when the use of morphine is associated with abdominal pain.

Diamorphine (di-acetylmorphine; not USA) is, in effect, a pro-drug for morphine which is de-acetylated by digestive juices and body fluids. Thus, *advice for morphine applies equally to diamorphine.*

Buprenorphine is only partly hepatically metabolized and in theory, can be used cautiously in patients with cirrhosis. However, it is highly protein bound, has a variable halflife and a post-marketing study of IV use has shown higher plasma levels in patients with moderate−severe hepatic impairment. Two thirds of buprenorphine are eliminated unchanged in the feces, which could be relevant in patients with cholestatic disease. Further, although the active metabolite (norbuprenorphine) does not usually exert a central effect, this may change in situations where the blood brain barrier becomes more permeable (see above). SL use is contra-indicated in severe hepatic impairment and TD use is not recommended (see above).

Fentanyl pharmacokinetics are not altered in patients with cirrhosis after a single IV dose.[27] However, in severe hepatic impairment, fentanyl clearance is significantly reduced when administered CIVI.[28] With TD patches, the overall exposure to fentanyl is increased (AUC and C_{max} increased by 75% and 35% respectively), although the halflife following removal is unchanged.[24] Fentanyl is highly protein bound and almost exclusively metabolized by the liver. It has a large volume of distribution and only a relatively small fraction is available in the central compartment for hepatic uptake. Thus, clearance is mostly affected by changes in hepatic blood flow rather than reduced metabolism.

Alfentanil pharmacokinetics can be altered even in *mild* hepatic impairment.[24] Alfentanil is highly protein bound, it has a lower volume of distribution than fentanyl and is metabolized almost exclusively by the liver.

Hydromorphone undergoes significant first-pass hepatic metabolism. In *moderate* hepatic impairment, because of increased bio-availability, both C_{max} and the AUC for PO hydromorphone are quadrupled, although surprisingly the halflife is unchanged. Thus, if used, low starting doses at standard time intervals are advisable.[24,29] With severe hepatic impairment, the halflife will almost certainly increase, and the frequency of dosing should also be reduced. Parenterally, no data are available; based on pharmacokinetic parameters, parenteral hydromorphone may be safer than PO. Hydromorphone has low protein binding, a short halflife and a relatively large volume of distribution and the SPC suggests lower doses can be used with caution in hepatic impairment. However, the main metabolite, hydromorphone-3-glucuronide, has no analgesic activity, but is a potent neuro-excitant and is renally excreted. Thus, hydromorphone should be avoided in hepatorenal syndrome.

For both PO and parenteral oxycodone, in severe hepatic impairment due to cirrhosis, the AUC and halflife are significantly increased, and the clearance decreased.[24,30] Thus, both PO and parenteral oxycodone are contra-indicated by the manufacturer in this setting; if use is unavoidable, both the dose and frequency of administration should be reduced.

The use of methadone requires specialist supervision because of the inherent risks of accumulation and toxicity even in patients without hepatic impairment. In addicts receiving methadone maintenance, severe hepatic impairment increases halflife, but AUC and clearance are unchanged.[24] There are no data for the analgesic use of methadone. However, variability in bio-availability, high protein binding and significant hepatic metabolism are likely to further complicate its use in severe hepatic impairment and it is best avoided.

Choice of opioid analgesic

The use of codeine, dihydrocodeine (not USA) and tramadol are best avoided in severe hepatic impairment.

In some liver units, fentanyl SC/CSCI is the first-line choice in patients with severe hepatic impairment, particularly when there is concurrent renal impairment.[7] Transmucosal fentanyl products may be an alternative option for break-through pain in those patients who have achieved the necessary degree of opioid tolerance.

The cautious use of PO immediate-release morphine is a reasonable option, using lower starting doses and decreased dosing frequency. Generally, SR products should be avoided. However, if continued regular use of immediate-release morphine is without problem, an SR morphine product may be tried cautiously.

Table 4
Opioid analgesics in severe hepatic impairment. Before use, see introductory and class specific text above

Drug[a,b]	PO bio-availability (%)	Protein-binding (%)	Halflife in normal liver function (h)	Significant hepatic metabolism	Significant biliary excretion of drug ± active metabolite(s)	Increase in halflife in severe hepatic impairment	Dose and comments
Generally safer							
Fentanyl	N/A	80–85	4–16 (injection)	Yes; see text	No	No	Lower doses may be sufficient SC: start with 12.5–25 microgram q1h p.r.n. CSCI: start with 100–150 microgram/24h
Use cautiously							
Buprenorphine[c]	50 (SL)	96	3–16 (injection) 20–25 (SL)	No; but see text	Yes (66%)	Probably ↑	SL/SC: reduce initial dose by 25–50%
Diamorphine (not USA)	No data	No data	3min (IV); ≤5h[d]	See morphine	See morphine	No	*Pro-drug:* see text; SC: start with 1.25–2.5mg q2–4h p.r.n CSCI: start with 5mg/24h
Morphine	15–64	20–35	2–5	Yes; active metabolite	Yes; see text	<100%	PO: start with 5mg q8–6h and q2–4h p.r.n. SC: start with 2.5mg q2–4h p.r.n. CSCI: start with 10mg/24h
Avoid if possible							
Alfentanil	N/A	92	1.5	Yes	No	Yes	If unavoidable: SC: start with 50–100 microgram q1h p.r.n. CSCI: start with 0.5–1mg/24h
Codeine	12–84	7	3–4	Yes; active metabolite	No	Yes	*Pro-drug:* reduced bio-transformation and thus reduced/

(*Continued*)

Table 4
Continued

Drug[a,b]	PO bio-availability (%)	Protein-binding (%)	Halflife in normal liver function (h)	Significant hepatic metabolism	Significant biliary excretion of drug ± active metabolite(s)	Increase in halflife in severe hepatic impairment	Dose and comments
							unpredictable effect
Dihydrocodeine (not USA)	20	No data	3.5–5	Yes; active metabolite	No data	Probably ↑	See text
Hydromorphone	32	<10	2.5	Yes; neurotoxic metabolite	No	Probably ↑	If unavoidable: decrease frequency of PO/SC immediate release products to q8h
*Methadone[c]	40–100	60–90	5–130	Yes	Possible	Probably ↑	*Specialist use only* Requires careful and *slow* titration; accumulation occurs even without hepatic impairment[7]
Oxycodone	60–87	45	2–4	Yes; active metabolite	No	<400%	If unavoidable: PO: start with 2.5mg q8h and q2–4h p.r.n. SC: start with 1.5mg q2–4h p.r.n. CSCI: start with 5mg/24h
Tramadol	90 (multiple doses)	20	6	Yes; active metabolite	No	<300%	*Pro-drug:* reduced bio-transformation and thus reduced/unpredictable effect

*Specialist use only
[a]whichever drug is used, because of the altered pharmacodynamic effects of opioids in severe hepatic impairment, a slower than usual titration and close monitoring of the patient is required
[b]avoid SR and TD products (see text)
[c]because of the long halflife and time taken to reach steady state, undesirable effects with these opioids may only become apparent after several days or weeks of regular use
[d]active metabolite.

Antidepressants (Table 5)

Regardless of the pharmacokinetic changes described below, in severe hepatic impairment antidepressants with sedative ± constipating effects can cause, worsen or sometimes mask encephalopathy. A slower than usual titration and close monitoring of the patient is required.

Concurrent use of other drugs with sedative ± constipating effects, e.g. opioids, further increases the risk of toxicity.

Pharmacokinetic changes

Most antidepressants are highly protein bound and hepatically metabolized by one or more CYP450 enzymes. Metabolism will be further impaired in, e.g. amitriptyline, nortriptyline (CYP2D6), amitriptyline, citalopram and sertraline (CYP2C19), and the risk of toxicity increased from a pharmacokinetic drug–drug interaction involving an inhibitor of the CYP450 enzyme(s).

Because of the time taken to accumulate, undesirable effects may become apparent only after days or weeks of regular use for those antidepressants with long halflives, e.g. amitriptyline, citalopram, mirtazapine, nortriptyline and sertraline.

TCAs are not a first-line treatment for depression. In palliative care, amitriptyline is used for neuropathic pain, its halflife does not appear to increase in severe hepatic impairment.

All SSRIs accumulate in severe hepatic impairment.[31] Sertraline has very high first-pass metabolism and protein binding, citalopram less so, but is more dependent on biliary excretion for elimination.[15] Both have significantly increased halflives in severe hepatic impairment. Citalopram accumulation will increase the risk of prolongation

of the QT interval (and thereby risk of ventricular arrhythmia. The pharmacokinetic profiles of fluoxetine, fluvoxamine and paroxetine are no more favorable in severe hepatic impairment and they are also strong hepatic enzyme inhibitors.

The clearance of mirtazapine is reduced in *mild* hepatic impairment and plasma concentration increases; accumulation also occurs in end-stage *renal* impairment.[17] Thus, mirtazapine is not a good choice in hepatorenal syndrome.

Trazodone is not a first-line treatment for depression in palliative care. It undergoes extensive hepatic metabolism and has been associated with severe hepatotoxicity.

The halflife of venlafaxine is prolonged even in *mild* hepatic impairment but with a large degree of intersubject variation. The halflife of duloxetine more than doubles in *moderate* hepatic impairment, and the AUC almost quadruples. Thus, both are best avoided. Further, both venlafaxine and duloxetine accumulate in end-stage *renal* impairment, making neither a good choice in hepatorenal syndrome.[17]

Choice of antidepressant

Of the SSRIs generally used in palliative care, the cautious use of citalopram is probably the best choice for patients with severe hepatic impairment, unless they are have additional risk factors for QT prolongation or severe cholestasis. Because SSRIs decrease platelet aggregation and increase the risk of GI bleeding, they are not a good choice in patients with coagulopathy or esophageal varices. Although sertraline is generally best avoided, it is used for cholestatic pruritus.

Cautious use of mirtazapine may also be an option and has a lower risk of bleeding than an SSRI. It should be avoided in patients with hepatorenal syndrome and discontinued if jaundice occurs. It is more sedating and associated with less nausea than SSRIs and is used in some liver units because of its beneficial effects on appetite and sleep.[31]

Amitriptyline may be used with caution for neuropathic pain. The presence of cardiac co-morbidity will limit its use.

Table 5
Antidepressants in severe hepatic impairment. Before use, see introductory and class specific text above

Drug[a]	PO bio-availability (%)	Protein-binding (%)	Halflife in normal liver function (h)	Significant hepatic metabolism	Significant biliary excretion of drug ± active metabolite(s)	Increase in halflife in severe hepatic impairment	Dose and comments
Use cautiously							
Amitriptyline[b]	45	96	9–25	Yes; active metabolite	No	No	PO: start with 5–10mg at bedtime *Not a first-line treatment for depression*
Citalopram[b]	80	<80	36	Yes; active metabolite	Yes (85%)	>200%	PO: start with 10mg once daily; maximum dose 16mg (oral solution) or 20mg (tablet) once daily
Mirtazapine[b]	50	85	20–40	Yes; active metabolite	No	Probably ↑	PO: start with 15mg at bedtime maximum dose 30mg at bedtime
Avoid if possible							
Duloxetine	90	96	8–17	Yes	No	>200%	See text
Sertraline[b]	>44	98	26	Yes	No	>300%	Avoid unless for cholestatic pruritus: PO: start with 50mg once daily, maximum 100mg once daily (see text)
Trazodone	65	89–95	5–13 (doubles in elderly)	Yes; active metabolite	No	Probably ↑	*Not a first-line treatment for depression*
Venlafaxine[c]	13 (45 SR)	27	5 (11)[d]	Yes; active metabolite	No	Yes	See text; if unavoidable, PO: start with 37.5mg once daily

[a]whichever drug is used, because of the altered pharmacodynamic effects of antidepressants in severe hepatic impairment, a slower than usual titration and close monitoring of the patient is required
[b]because of the long halflife and time taken to reach steady state, undesirable effects with these antidepressants may only become apparent after several days or weeks of regular use
[c]avoid use SR products
[d]active metabolite.

Anti-emetics (Table 6)

Regardless of the pharmacokinetic changes described below, in severe hepatic impairment anti-emetics with sedative ± constipating effects can cause, worsen or sometimes mask hepatic encephalopathy. A slower than usual titration and close monitoring of the patient is required.

Concurrent use of other drugs with sedative ± constipating effects, e.g. opioids, further increases the risk of toxicity.

Pharmacokinetic changes

For anti-emetics metabolized via CYP450, e.g. domperidone (not USA), haloperidol and ondansetron, there is an increased risk of toxicity from a drug−drug interaction with the concurrent use of an inhibitor of the relevant CYP450 enzyme.

The risk of prolongation of the QT interval (and thereby risk of ventricular arrhythmia) is higher with domperidone, haloperidol, levomepromazine (methotrimeprazine; not USA) and ondansetron. The risk may be increased as a result of, e.g. drug accumulation, drug−drug interaction, concurrent use of other drugs that either prolong the QT interval or cause electrolyte imbalance.

Because of the time taken to accumulate, undesirable effects may become apparent only after days or weeks of regular use, for those anti-emetics with a long halflife, e.g. cyclizine, haloperidol and levomepromazine.

Domperidone has the advantage of not crossing the blood-brain barrier. However, in moderate hepatic impairment the AUC increases 3-fold, the C_{max} and halflife increase 1.5-fold and the unbound fraction by 25%. Thus, the SPC contra-indicates use in moderate−severe hepatic impairment.

In severe hepatic impairment, the halflife of metoclopramide increases by >100% necessitating a dose reduction.[32,33] Similarly, clearance of ondansetron is reduced and the maximum dose limited.[34]

Although rare, haloperidol, levomepromazine and prochlorperazine (antipsychotic type anti-emetics) can cause hepatotoxicity (see Antipsychotics below).

Choice of anti-emetic

Domperidone is the anti-emetic of choice in many liver units in the UK, despite the SPC contra-indication.[35] The starting dose should be halved and the risk/benefit assessed in patients with additional risk factors for QT prolongation. Metoclopramide and ondansetron are also commonly used in reduced doses. Note. Ondansetron is constipating and an increased dose of laxatives may be required.

Table 6

Anti-emetics in severe hepatic impairment. Before use, see introductory and class specific text above

Drug[a]	PO bio-availability (%)	Protein-binding (%)	Halflife in normal liver function (h)	Significant hepatic metabolism	Significant Biliary excretion of drug ± active metabolite(s)	Increase in halflife in severe hepatic impairment	Dose and comments
Use cautiously							
Domperidone (not USA)[b]	12−18	>90	7−9	Yes	No	50%	PO: start with 5mg b.i.d., maximum 10mg t.i.d..
Metoclopramide[b]	50−80	13−22	4−6	Yes	No	>100%	PO/SC: start with 5mg b.i.d., maximum 10mg b.i.d.− t.i.d..
Ondansetron	56−71	70−76	3−6	Yes	No data	>300%	PO/SC: maximum 8mg/24h
Avoid if possible							
Cyclizine[c]	50%	No data	20	Yes	No data	No data	If unavoidable, PO: start with 50mg b.i.d. SC: start with 25mg b.i.d.
Haloperidol[c]	45−75	92	12−38	Yes; active metabolite	Possible	No data	If unavoidable PO/SC: start with 500microgram.at bedtime and q4h p.r.n. *Also see Anti-psychotics Table 8*
Levomepromazine (methotrimeprazine; not USA)[c]	20−40	No data	15−30	Yes; active metabolite	No data	No data	If unavoidable, PO/SC: start with 2.5−3.125mg at bedtime and q4h p.r.n. *Also see Anti-psychotics Table 8*
Prochlorperazine[c]	6	96	15−20	Yes	No data	Probably ↑	If unavoidable Buccal: start with 3mg b.i.d. PO: start with 5mg t.i.d..

[a]whichever drug is used, because of the altered pharmacodynamic effects of anti-emetics in severe hepatic impairment, a slower than usual titration and close monitoring of the patient is required

[b]domperidone and metoclopramide should be used at the lowest effective dose for the shortest possible time because of concerns over prolonged QT interval or drug-induced movement disorders respectively

[c]because of the long halflife and time taken to reach steady state, undesirable effects with these anti-emetics may only become apparent after several days or weeks of regular use.

Anti-epileptics (Table 7)

Regardless of the pharmacokinetic changes described below, in severe hepatic impairment anti-epileptics with sedative effects may cause, worsen or sometimes mask encephalopathy. A slower than usual titration and close monitoring of the patient is required.

Concurrent use of other drugs with sedative ± constipating effects, e.g. opioids, further increases the risk of toxicity.

Pharmacokinetic changes

Of the anti-epileptics generally used in palliative care, the following should be considered in severe hepatic impairment:

- reduced protein-binding affects the most highly protein-bound, e.g. phenytoin and valproate (for monitoring purposes, or when toxicity is suspected, the free fraction plasma concentration should be measured)
- all but levetiracetam, oxcarbazepine and gabapentin/pregabalin are dependent on CYP450
- the risk of toxicity is also greater from a pharmacokinetic drug–drug interaction involving an inhibitor of CYP450 or other enzymes responsible for metabolism of the anti-epileptic, e.g.:
  - ➢ CYP3A4 inhibitors will lead to reduced metabolism of carbamazepine; CYP2C9 inhibitors, of phenobarbital and phenytoin; and CYP2C19 inhibitors, of phenytoin
  - ➢ valproate, by inhibiting epoxide hydrolase, may reduce the metabolism of carbamazepine.

Because of the time taken to accumulate, undesirable effects may become apparent only after days or weeks of regular use for those anti-epileptics with a long halflife, e.g. carbamazepine, clonazepam, phenobarbital and phenytoin.

Oxcarbazepine is a pro-drug which is rapidly converted in the liver to an active metabolite. The pharmacokinetics of oxcarbazepine and the metabolite are unchanged in mild–moderate hepatic impairment, but reduced biotransformation should be anticipated in severe impairment.

Because phenytoin is highly protein-bound, there is a danger of toxicity if the dose is not adjusted when a patient is hypo-albuminemic or is jaundiced. Phenobarbital is rarely used as an anti-epileptic in palliative care. In a single dose study, the halflife of phenobarbital increased from 86h to 130h in cirrhosis.[36] Because both phenytoin and phenobarbital should be avoided in patients with severe *renal* impairment, neither are a good choice in hepatorenal syndrome.[17]

Levetiracetam, gabapentin and pregabalin are not hepatically metabolized or excreted, in addition they have low protein binding and short halflives. Thus, they are a favorable choice in hepatic impairment. However, all require slow titration from low doses to minimize the sedative effects and dose reduction if *renal* impairment is present.

Carbamazepine and valproate have been associated with hepatotoxicity and should be avoided if possible (see Drug-induced hepatotoxicity above).

Choice of anti-epileptic

Levetiracetam is a good first-line choice for the long-term management of patients with a broad range of seizure types who also have severe hepatic impairment. It may also have a role in status epilepticus, when benzodiazepines are insufficient. However, it is renally excreted and a dose reduction is required when there is concurrent *renal* impairment.[17]

Gabapentin and pregabalin are also a good choice for long-term use as an anti-epileptic or for neuropathic pain. Start with low doses and titrate slowly to reduce the risk of sedative effects; for patients with *renal* impairment, the dose may need to be further reduced.[17]

Table 7

Anti-epileptics in severe hepatic impairment. Before use, see introductory and class specific text above

Drug[a]	PO bio-availability (%)	Protein-binding (%)	Halflife in normal liver function (h)	Significant hepatic metabolism	Significant Biliary excretion of drug ± active metabolite(s)	Increase in halflife in severe hepatic impairment	Dose and comments
Generally safer							
Gabapentin	30–75	<3	5–7	No	No	No data	Use low doses and titrate slowly PO: start with 100mg at bedtime, increase by 100mg/24h every 2–3 days; dose may need to be adjusted according to renal function (see text)

(*Continued*)

Table 7
Continued

Drug[a]	PO bio-availability (%)	Protein-binding (%)	Halflife in normal liver function (h)	Significant hepatic metabolism	Significant Biliary excretion of drug ± active metabolite(s)	Increase in halflife in severe hepatic impairment	Dose and comments
Levetiracetam	≥95	<10	6–8	No	No	No data	PO/IV: start with 250mg b.i.d.; dose may need to be adjusted according to renal function (see text)
Pregabalin	≥90	0	5–9	No	No	No data	Use low doses and titrate slowly PO: start with 25–50mg b.i.d.: dose may need to be adjusted according to renal function (see text)
Use cautiously							
Oxcarbazepine	≥95	40–60 metabolite	1–3 (metabolite 9)	Yes; active metabolite	No	No data	*Pro-drug:* reduced bio-transformation and thus reduced/unpredictable effect; PO: start with 75mg b.i.d.
Avoid if possible							
Carbamazepine[b]	85–100	70–80	16–36	Yes; active metabolite	Possible	No data	If unavoidable, PO: start with 50mg b.i.d.
Clonazepam[b]	90	86	20–60	Yes; active metabolite	No	No data	*Not a first-line treatment for seizures* Also see Benzodiazepines, Table 9
Phenobarbital[b]	≥90	45–60	75–120	Yes	No data	<50%	If unavoidable, use only with specialist neurological supervision
Phenytoin[b]	90–95	90	20–60	Yes	Possible	No data	If unavoidable, monitor plasma levels adjusted for hypo-albuminemia
Valproate	95	90–95	6–20	Yes	No	No data	If unavoidable, start with low dose, titrate slowly

[a]whichever drug is used, because of the altered pharmacodynamic effects of anti-epileptics in severe hepatic impairment, a slower than usual titration and close monitoring of the patient is required
[b]because of the long halflife and time taken to reach steady state, undesirable effects with these anti-epileptics may only become apparent after several days or weeks of regular use.

Antipsychotics (Table 8)

Regardless of the pharmacokinetic changes described below, in severe hepatic impairment antipsychotics with sedative ± constipating effects of can cause, worsen or sometimes mask encephalopathy. A slower than usual titration and close monitoring of the patient is required.

Concurrent use of other drugs with sedative ± constipating effects, e.g. opioids, further increases the risk of toxicity.

Pharmacokinetic changes

There are limited data on antipsychotics, the following should be borne in mind:

- *all* the featured antipsychotics are highly protein bound
- *all* the featured antipsychotics are extensively metabolized in the liver and dependent on one or more of CYP3A4, CYP2D6, and CYP1A2; the risk of toxicity is greater from a pharmacokinetic drug-drug interaction with inhibitors of the relevant CYP450, e.g. haloperidol, quetiapine, risperidone (CYP3A4), haloperidol and risperidone (CYP2D6), and olanzapine (CYP1A2).

Undesirable effects may become apparent only after days or weeks of regular use for those antipsychotics with long halflives, e.g. haloperidol, olanzapine, risperidone. Concurrent use of other drugs with CNS depressant activity, e.g. opioids, increases the risk of toxicity.

The risk of prolongation of the QT interval (and thereby risk of ventricular arrhythmia) may be higher with haloperidol and lowest for quetiapine. The risk may be increased as a result of, e.g. drug accumulation, drug–drug interaction, concurrent use of other drugs that either prolong the QT interval or cause electrolyte imbalance.

Olanzapine has a long halflife and only moderate PO bio-availability. Based on this, a lower starting dose is recommended, only increasing with caution.

The halflife of risperidone was not significantly increased in patients with severe hepatic impairment. However, despite normal plasma levels, the free (unbound) fraction was increased by about 40%. Thus, lower doses are needed in severe hepatic impairment. The clearance of risperidone is reduced in *moderate renal* impairment.[17] Thus, it is not a good choice in hepatorenal syndrome.

Quetiapine has a short halflife. Clearance is reduced by 25% in patients with stable alcoholic cirrhosis, thus lower doses are needed.

Antipsychotics can be associated with increased LFTs; rarely, significant hepatotoxicity can occur.[37]

Choice of antipsychotic

Generally, the long-term use of antipsychotics should be avoided in severe hepatic impairment.[31] If unavoidable, based on pharmacokinetic parameters, quetiapine is the best choice for the long-term treatment of psychosis, mania and bipolar disorder.

For the long-term use of antipsychotics as anti-emetics, see Anti-emetics section and Table 6. For the short-term use of antipsychotics in the last days of life, see Box D below.

Table 8
Antipsychotics in severe hepatic impairment. Before use, see introductory and class specific text above

Drug[a]	PO bio-availability (%)	Protein-binding (%)	Halflife in normal liver function (h)	Significant hepatic metabolism	Significant biliary excretion of drug ± active metabolite(s)	Increase in halflife in severe hepatic impairment (h)	Dose and comments
Use cautiously							
Olanzapine[b]	60	93	34 (52 elderly)	Yes	Possible	No data	PO: start with 2.5–5mg at bedtime
Quetiapine[c]	100	83	6–14	Yes; active metabolite	No	Probably ↑	PO: start with 12.5mg b.i.d.; increase daily by 12.5mg
Risperidone[b]	99	90	20[d]	Yes; active metabolite	No	No	PO: start with 500microgram at bedtime; increase by 500microgram every 3–4 days
Avoid if possible							
Haloperidol[b]	45–75	92	12–38	Yes; active metabolite	Possible	No data	If unavoidable PO/SC: start with 500microgram at bedtime and q4h p.r.n. *Also see Anti-emetics Table 6*
Levomepromazine (methotrimeprazine; not USA)[b]	20–40	No data	15–30	Yes; active metabolite	No data	No data	*Not a first-line treatment for psychosis* *Also see Anti-emetics Table 6*

[a]whichever drug is used, because of the altered pharmacodynamic effects of antipsychotics in severe hepatic impairment, a slower than usual titration and close monitoring of the patient is required
[b]because of the long halflife and time taken to reach steady state, undesirable effects with these antipsychotics may only become apparent after several days or weeks of regular use
[c]avoid SR products
[d]total for the parent drug and active metabolite.

Benzodiazepines and Z-drugs (Table 9)

Regardless of the pharmacokinetic changes described below, in severe hepatic impairment the sedative effects of benzodiazepines and Z-drugs can cause, worsen or sometimes mask encephalopathy.[38,39] A slower than usual titration and close monitoring of the patient is required.

Concurrent use of other drugs with CNS depressant ± constipating effects, e.g. opioids, further increases the risk of toxicity.

Pharmacokinetic changes

Of the featured benzodiazepines and Z-drugs generally used long-term in palliative care, all are significantly hepatically metabolized and contra-indicated in severe hepatic impairment. For those drugs metabolized by CYP450 enzymes, e.g. diazepam, zopiclone, the risk of toxicity is greater from a pharmacokinetic drug–drug interaction involving an inhibitor of CYP450. Further, all the featured benzodiazepines (but not zopiclone) are highly protein bound.

Because of the time taken to accumulate, undesirable effects may become apparent only after days or weeks of regular use for those benzodiazepines with a long halflife, e.g. clonazepam, diazepam.

Although the halflife of lorazepam has been shown to double in cirrhosis, plasma clearance was *not* affected. The increased halflife is explained by an increased volume of distribution, caused by a reduction in plasma protein-binding.[39]

Temazepam is metabolized by direct conjugation and is not dependent on CYP450 metabolism, which may explain why the halflife is little changed in cirrhosis.[39,40]

The halflife of diazepam in healthy subjects is very long (≤5 days, with an active metabolite halflife of ≤8 days). In cirrhosis this more than doubles.[41]

Zopiclone is hepatically metabolized by CYP3A4. Although the halflife is relatively short in comparison to other sedatives, in patients with cirrhosis it more than doubles.[42] The SPC states that plasma clearance of zopiclone is delayed by 40%.

Choice of benzodiazepine or Z-drug

Generally, the use of benzodiazepines or Z-drugs as sedatives or anxiolytics should be avoided in severe hepatic impairment. If unavoidable, limit their use to the short-term, ideally <1 week. Based on pharmacokinetic parameters, zopiclone may be a reasonable choice as a night sedative and lorazepam as an anxiolytic. Lorazepam is also used short-term to manage alcohol withdrawal symptoms, seek hepatology advice.[43]

For other indications, e.g. myoclonus, restless leg syndrome, muscle spasm, prophylaxis of seizures, longer-acting benzodiazepines (e.g. clonazepam, diazepam) should be generally avoided because they are not a first-line choice in these settings and have unfavorable pharmacokinetics in severe hepatic impairment.

For the use of midazolam in the last days of life, see Box D below.

Table 9

Benzodiazepines and Z-drugs in severe hepatic impairment. Before use, see introductory and class specific text above

Drug[a]	PO bio-availability (%)	Protein-binding (%)	Halflife in normal liver function (h)	Significant hepatic metabolism	Significant biliary excretion of drug ± active metabolite(s)	Increase in halflife in severe hepatic impairment (h)	Dose and comments
Use cautiously							
Lorazepam[b]	90	85	10–20	Yes	No	See text	SL/PO: start with 500microgram/24h
Zopiclone	75	45–80	5	Yes; active metabolite	No	>100%	PO: start with 3.75mg at bedtime
Avoid if possible							
Clonazepam[b]	90	86	20–60	Yes; active metabolite	No	No data	See text; *also see Anti-epileptics, Table 7*
Diazepam[b]	90	95–99	25–50 (≤200[c])	Yes; active metabolites	No	>100%	See text
Temazepam	90	96	8–15	Yes	No	No	If unavoidable PO: start with 5mg at bedtime

[a]whichever drug is used, because of the altered pharmacodynamic effects of benzodiazepines and Z-drugs in severe hepatic impairment, a slower than usual titration and close monitoring of the patient is required

[b]because of the long halflife and time taken to reach steady state, undesirable effects with these benzodiazepines and Z-drugs may only become apparent after several days or weeks of regular use

[c]active metabolite.

Miscellaneous-drugs (Table 10)

Regardless of the pharmacokinetic changes described below, in severe hepatic impairment drugs with sedative ± constipating effects can cause, worsen or sometimes mask encephalopathy. A slower than usual titration and close monitoring of the patient is required.

Concurrent use of other drugs with CNS depressant ± constipating effects, e.g. opioids, further increases the risk of toxicity.

The relative safety and dose adjustments for other common palliative care drugs for long-term use in severe hepatic impairment are shown in Table 10.

PPIs are generally preferred to H_2-receptor antagonists. In patients with cirrhosis, it is recommended that PPI use be limited to specific indications, e.g. peptic ulcer disease, because of concerns of a possible association with poorer outcomes (e.g. increased risk of spontaneous bacterial peritonitis, hepatic encephalopathy and mortality).[44,45] In cirrhosis, there is a significant increase in overall exposure to lansoprazole and, to a lesser extent, omeprazole, leading some to recommend against their respective use in mild and severe hepatic impairment.[44] However, in practice, both have been used in severe hepatic impairment in lower PO doses.

When indicated, ranitidine (the *PCF* H_2 antagonist of choice) has a favorable pharmacokinetic profile in severe hepatic impairment. It is not extensively hepatically metabolized, has a short halflife and low protein binding. However, dose reduction is needed with concurrent *renal* impairment.

Antidiarrheals, e.g. loperamide, should generally be avoided in severe hepatic impairment because of the risk of causing, worsening or masking encephalopathy from their constipating effect. Further, loperamide is extensively hepatically metabolized, with most of the drug removed by first pass metabolism. Thus, severe hepatic impairment may result in an increase in plasma levels of loperamide, increasing the risk of prolonged QT interval and CNS toxicity.

There is a lack of pharmacokinetic data for antimuscarinic drugs in severe hepatic impairment. Unlike scopolamine (hyoscine) *hydrobromide* (which should be avoided), scopolamine *butylbromide* and glycopyrrolate (glycopyrronium) do not generally cross the blood-brain barrier. However, because of the lack of data, potential for greater CNS penetration and their constipating effects, both scopolamine *butylbromide* and glycopyrrolate should be used cautiously in severe hepatic impairment. For the use of antimuscarinics for noisy rattling breathing at the end of life, see Box D below.

Despite the lack of data, based on their favorable pharmacokinetic profile, bisphosphonates can be used in severe hepatic impairment. They are not hepatically metabolized but are renally excreted. Reduced doses are required in patients with concurrent *renal* impairment, with ibandronic acid associated with less renal toxicity than other bisphosphonates.[17,46] Denosumab is an alternate osteoclast inhibitor that is generally safe in both hepatic and renal impairment.[47]

Full data for laxatives have not been included. Generally, they are not absorbed and can be used in usual doses. Laxatives should be routinely prescribed and carefully titrated against bowel movement for patients taking opioids to minimize the risk of constipation. Lactulose and polyethylene glycols (macrogols) are used in the treatment of hepatic encephalopathy (see Simplifying long-term hepatic drugs below).

Of the skeletal muscle relaxants used long-term, baclofen has a favorable pharmacokinetic profile in severe hepatic impairment. However, it should be used cautiously, with lower starting doses, because of its sedative properties. Further, toxicity can occur in moderate–severe *renal* impairment. Because tizanidine is extensively hepatically metabolized and can cause hepatotoxicity in high doses (see Drug-induced hepatotoxicity above) it should be avoided.

Systemic corticosteroids are generally mostly hepatically metabolized. Because of their salt and water retaining properties, they can cause or worsen ascites. They also have the potential to cause or worsen encephalopathy, and to increase the risk of GI bleeding in patients with coagulopathy or esophageal varices (see Box B). Thus, dexamethasone, the most frequent systemic corticosteroid used in palliative care, should be used cautiously at the lowest effective dose.

The halflife of octreotide may be increased in cirrhosis and the SPC recommends adjusting the maintenance dose in these patients. Octreotide has an inhibitory effect on gallbladder motility and bile secretion; the clinical relevance of this in this setting is uncertain.

Spironolactone is authorized in hepatic cirrhosis with ascites and edema. The dose can generally be given once daily because of the significantly increased halflife in cirrhosis.[48] Because of the risk of electrolyte imbalance (particularly hyperkalemia and hyponatremia), close monitoring is required.

Table 10

Miscellaneous drugs in severe hepatic impairment. Before use, see introductory and class specific text above

Drug[a]	PO bioavailability (%)	Protein-binding (%)	Halflife in normal liver function (h)	Significant hepatic metabolism	Significant biliary excretion of drug ± active metabolite(s)	Increase in halflife in severe hepatic impairment (h)	Relative safety	Dose and comments
Acid suppressants								
Lansoprazole	80–90	97	1–2	Yes	No	<500%	**Use Cautiously**	See text. PO: start with 15mg once daily; maximum dose 30mg once daily
Omeprazole	60	95	0.5–3	Yes	No	See text	**Use Cautiously**	PO: start with 10mg once daily; maximum dose 20mg once daily
Ranitidine	50	15	2–3	No	No	No data	**Generally safer**	Dose unchanged; may need adjustment according to renal function

(*Continued*)

Table 10
Continued

Drug[a]	PO bio-availability (%)	Protein-binding (%)	Halflife in normal liver function (h)	Significant hepatic metabolism	Significant biliary excretion of drug ± active metabolite(s)	Increase in halflife in severe hepatic impairment (h)	Relative safety	Dose and comments
Antidiarrheals								
Loperamide	<1	80	9–14	Yes	No	No data	**Avoid**	If unavoidable; PO: start with 2mg stat
Antimuscarinics								
Glycopyrrolate (Glycopyrronium)	<5	No data	1–1.5	Possible	Possible	No data	**Use cautiously**	SC: start with 200microgram q2h p.r.n. CSCI: start with 600microgram/24h
Scopolamine (hyoscine) *butylbromide*	<1	4	1–5	Possible	No data	No data	**Use cautiously**	SC: start with 20mg q1h p.r.n. CSCI: start with 60mg/24h
Bisphosphonates and denosumab								
Bisphosphonates	N/A	Variable	N/A	No	No	No data	**Generally safer**	Dose unchanged; may need adjustment according to renal function (see text)
Denosumab	N/A	Variable	N/A	No	No	No data	**Generally safer**	Dose unchanged
Laxatives	N/A	N/A	N/A	N/A	N/A	N/A	**Generally safer**	Dose unchanged
Skeletal muscle relaxants								
Baclofen	>90	30	3–4	No	No	No data	**Use Cautiously**	PO: start with 5mg once daily; dose may need adjustment according to renal function (see text)
Tizanidine	40	30	3	Yes	No	Probably ↑	**Avoid**	See text
Systemic corticosteroids								
Dexamethasone	78	77	4.5	Yes	No	Yes	**Use Cautiously**	PO: start with 2–16mg once daily according to indication
Other								
Octreotide	N/A	65	1.5	Yes	Possible	Yes	**Use Cautiously**	SC: lower maintenance doses may be sufficient
Spironolactone	60–90	90	1.5 (14–17)[b]	Yes; active metabolites	Possible	<600%	**Use Cautiously**	PO: once daily dose; monitor electrolytes closely

[a]whichever drug is used, because of the altered pharmacodynamic effects in severe hepatic impairment, a slower than usual titration and close monitoring of the patient is required
[b]active metabolite.

SIMPLIFYING LONG-TERM HEPATIC DRUGS

Patients may be taking long-term drugs to manage the various aspects of their liver disease, e.g. ascites, encephalopathy, pruritis (see below). Generally, these should be continued in patients with a primary diagnosis of end-stage liver disease when a liver transplant is a possible option. However, their ongoing necessity can be reviewed as the end of life approaches, e.g. in those with a primary diagnosis of end-stage liver disease for whom a liver transplant is not appropriate, and in those with severe hepatic impairment caused by incurable cancer. The decision of when to stop these drugs is informed by considering the:

- prognosis of the patient
- purpose of the drug
- degree of hepatic impairment
- risk of undesirable effects from continuing the drug vs. the likely effects from stopping it
- burden of taking tablets.

Prognosis of patients with end-stage liver disease is variable. Although median survival is about 2 years, death can be relatively sudden and unexpected. Median survival is reduced in the presence of:

- severe or refractory encephalopathy (12 months)
- refractory ascites (6 months)
- hepatorenal syndrome; type 2 (3–6 months), type 1 (2–4 weeks).[49]

The guidance below should be used in conjunction with specialist hepatology advice.

Antibiotic prophylaxis for spontaneous bacterial peritonitis

Prophylactic antibiotics, e.g. ciprofloxacin 500mg once daily, are used to reduce the high risk of bacterial peritonitis from a long-term indwelling ascitic drain or peritoneal catheter. These can be discontinued in the last weeks of life.

Antihypertensives

These should generally be discontinued in the last weeks of life, because of the risk of hypotension/falls and subdural bleeds, unless being taken for prophylaxis of variceal bleeding (see below).

Antiretrovirals

Generally, these are continued as long as the patient is able to take them. Discussion with local HIV teams is advised.

Diuretics for management of ascites

Management of ascites should focus on maintaining comfort and symptom control. Spironolactone ± furosemide PO are the diuretics of choice and should be continued if stopping is likely to exacerbate symptoms, and whilst the patient can tolerate PO tablets. They are generally discontinued in the last days of life. An ascitic drain can be considered for symptomatic relief.

Drugs for mineral and bone disease

Cirrhosis is a risk factor for osteoporosis and many patients may be taking calcium and vitamin D supplements. These can be discontinued.

Drugs for management of hepatic encephalopathy

Oral drugs for the management of hepatic encephalopathy, e.g. lactulose, polyethylene glycols (macrogol) 3350 (off-label) and rifaximin 550mg b.i.d. should be continued as long as possible and/or tolerated, with the aim of inducing bowel movements twice a day. Where PO treatment is not possible and administration via naso-gastric tube is inappropriate, the use of phosphate enemas may be considered.

Drugs for portal hypertension/prophylaxis of variceal bleeding

Where portal hypertension is being treated with beta-blockers, e.g. carvedilol, propranolol, these should be continued whilst the patient can tolerate PO tablets. ACE inhibitors should be stopped if renal function is poor, or when ascites develops.

Drugs for pruritis

Pruritis can be a debilitating symptom of cholestasis of any cause, including cirrhosis, causing discomfort, poor sleep and anxiety. Identification of cause is important and treatment for cholestatic-related pruritis should be continued if possible.[7]

Immunosupressants

Generally these are continued as long as the patient is able to take them. Discussion with hepatology/liver transplant teams is advised for those taking immunosuppressants who have previously undergone transplantation.

Thiamine and vitamin supplements

Patients with alcohol-related liver disease may be taking thiamine and other vitamin supplements. These can be discontinued.

Vitamin K

Vitamin K replacement should be limited to conscious patients with a reasonable performance status for whom other supportive measures are deemed appropriate, e.g. blood transfusion. Vitamin K should not be used in moribund patients in an attempt to prevent an imminent inevitable death.

LAST DAYS OF LIFE

Currently, there are no national guidelines for prescribing for patients with severe or end-stage hepatic impairment in the last days of life. Box D contains suggested starting doses for common symptoms based on consensus clinical experience. As the majority of drugs have CNS depressant effects ± cause constipation, one of the major challenges is to alleviate symptoms without precipitating or worsening encephalopathy. Thus, with all drugs, appropriate caution, close monitoring and individualized titration, initially with small doses, is required. Generally, SC p.r.n. injections are prescribed to facilitate this.

Box D. Anticipatory prescribing in patients with severe or end-stage hepatic impairment in the last days of life.

Starting doses given below are based on consensus clinical experience and take into account the risk of accumulation and toxicity; they may be lower than used in other circumstances. Generally, initial titration is with SC p.r.n. injections rather than CSCI.

Pain

In some liver units, fentanyl SC/CSCI is the first-line choice in patients with severe hepatic impairment, particularly when there is concurrent renal impairment (see Opioids section). However, it is uncertain if this outweighs the advantages of more cautious use of more familiar opioids in this setting. Starting dose in opioid-naïve patients:

- fentanyl 12.5–25microgram SC q1h p.r.n.
- morphine 2.5mg SC q1h p.r.n.

Breathlessness

Fentanyl can be used for breathlessness as well as pain; when there is concurrent anxiety combine with midazolam, e.g. 1–2.5mg SC q1h p.r.n.

Nausea and vomiting

Haloperidol 0.5–1mg SC q1h p.r.n.

Agitation, restlessness

Midazolam 1–2.5mg SC q1h p.r.n.

Delirium

Haloperidol ± midazolam, starting with similar doses and frequency to above.

Noisy rattling breathing

Scopolamine (hyoscine) *butylbromide* 20mg SC q1h p.r.n.

Abbreviations/key

AUC	Area under the plasma concentration–time curve
b.i.d.	Twice per day
CNS	Central Nervous System
CIVI	Continuous intravenous infusion
Cmax	Maximum plasma drug concentration
CSCI	Continuous subcutaneous infusion
CYP450	Cytochrome P450
dL	Decilitre(s)
g	Gram(s)
GI	Gastro-intestinal
H	Hour(s)
INR	International normalized ratio
IV	Intravenous
L	Litre(s)
LFT	Liver function test(s)
mg	Milligram(s)
micromol	Micromole(s)
min	Minute(s)
mL	Millilitre(s)
N/A	Not applicable
NSAID	Non-steroidal anti-inflammatory drug
PCF	Palliative Care Formulary

PI	Package insert (USA), equivalent to SPC (UK)
PO	Per os, by mouth
PPI	Proton pump inhibitor
PR	Per rectum
p.r.n.	As required
q1h, q8h	Every one hour, every eight hours etc
SC	Subcutaneous
SL	Sublingual
SPC	Summary of product characteristics (UK), equivalent to Package Insert (USA)
SR	Sustained-release; alternatives controlled-release, extended-release, modified-release (UK)
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
t.i.d..	Three times per day
TD	Transdermal

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