13 - Chapter 8 Prescribing in hepatic and renal impairm

01 - Hepatic impairment

Hepatic impairment

02 - General principles of prescribing in hepatic

General principles of prescribing in hepatic impairment

The Maudsley® Prescribing Guidelines in Psychiatry, Fifteenth Edition. David M. Taylor, Thomas R. E. Barnes and Allan H. Young. © 2025 David M. Taylor. Published 2025 by John Wiley & Sons Ltd. Chapter 8 Hepatic impairment Patients with hepatic impairment may have the following: ■ ■Reduced capacity to metabolise biological waste products, dietary proteins and foreign substances such as drugs. Clinical consequences include hepatic encephalopathy and increased dose-related adverse effects from drugs. ■ ■Reduced ability to synthesise plasma proteins and vitamin K-dependent clotting factors. Clinical consequences include hypoalbuminaemia, leading in extreme cases to ascites. Increased toxicity from highly protein-bound drugs should be anticipated. There is also an increased risk of bleeding from gastrointestinal irritant drugs and with selective serotonin reuptake inhibitors (SSRIs). ■ ■Reduced hepatic blood flow. Clinical consequences include oesophageal varices and elevated plasma levels of drugs that are subject to first-pass metabolism. General principles of prescribing in hepatic impairment Liver function tests (LFTs) are a poor marker of hepatic metabolising capacity. Many patients with chronic liver disease are asymptomatic or have fluctuating clinical symptoms. LFTs help evaluate hepatic damage but tell us little about hepatic function. There are few clinical studies relating to the use of psychotropic drugs in people with hepatic disease. The following principles should be adhered to:

1. Prescribe as few drugs as possible.
2. Use lower starting doses, particularly of drugs that are highly protein bound. Tricyclic antidepressants (TCAs), SSRIs (except citalopram), trazodone and Prescribing in hepatic and renal impairment

03 - Antipsychotics in hepatic impairment2

Antipsychotics in hepatic impairment2

754 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 8 antipsychotics may have increased free plasma levels, at least initially. This will not be reflected in measured (total) plasma levels. Use lower doses of drugs known to be subject to extensive first-pass metabolism. Examples include TCAs and haloperidol. 3. Be cautious with drugs that are extensively hepatically metabolised (most psychotropic drugs). Lower doses may be required. Exceptions are sulpiride, amisulpride, lithium and gabapentin, which all undergo no or minimal hepatic metabolism. 4. Leave longer intervals between dosage increases. The half-life of most drugs is prolonged in hepatic impairment and the duration of action is longer. Accumulation is more likely. Time to steady state is prolonged. 5. If albumin is reduced, consider the implications for drugs that are highly protein bound, and if ascites is present, consider the increased volume of distribution for water-soluble drugs. 6. Avoid medicines with a very long half-life or those that need to be metabolised to render them active (pro-drugs). 7. Always monitor carefully for adverse effects, which may be delayed. 8. Avoid drugs that are very sedative because of the risk of precipitating hepatic encephalopathy. 9. Avoid drugs that are very constipating because of the risk of precipitating hepatic encephalopathy. 10. Avoid drugs that are known to be hepatotoxic in their own right (e.g. monoamine oxidase inhibitors [MAOIs], chlorpromazine). Pre-existing liver disease does not increase the risk of drug--induced hepatotoxicity, but it may be more catastrophic if it does occur. 11. Choose a low-risk drug (see the tables in this section) and monitor LFTs weekly, at least initially. If LFTs deteriorate after a new drug is introduced, consider switching to another drug. Note that cross-hepatotoxicity between drugs is possible, especially if they are structurally related.1 These rules should always be observed in severe liver disease (low albumin, increased clotting time, ascites, jaundice, encephalopathy, etc.). The information here and following should be interpreted in the context of the patient's clinical presentation. Antipsychotics in hepatic impairment2 One-third of patients who are prescribed antipsychotic medication have at least one abnormal LFT and in 4% at least one LFT is elevated three times above the upper limit of normal.3 Transaminases are most often affected and this generally occurs within 1–6 weeks of treatment initiation.3 Only rarely does clinically significant hepatic damage result.3 Later in the treatment, the development of metabolic syndrome (obesity, insulin resistance) may be linked to the emergence of non-alcoholic fatty liver disease.4,5 Table 8.1 summarises antipsychotic medications used in hepatic impairment.

Prescribing in hepatic and renal impairment CHAPTER 8 Table 8.1 Antipsychotics in hepatic impairment. Drug Comments Amisulpride6–8 Predominantly renally excreted, so dosage reduction should not be necessary as long as renal function is normal. Uncommonly associated with rises in transaminases and rarely hepatocellular injury.9 Aripiprazole6,7,10,11 Extensively hepatically metabolised. Limited data that hepatic impairment has minimal effect on pharmacokinetics. Manufacturer states no dosage reduction required in mild to moderate hepatic impairment, but caution required in severe impairment. Small number of reports of hepatotoxicity, increased LFTs, hepatitis and jaundice.3,9,12–14 Asenapine6,7,11 Hepatically metabolised. Manufacturer advises to avoid use in severe hepatic disease (sevenfold increase in asenapine exposure). No dose adjustment required in mild to moderate disease,15 but be aware of the possibility of increased plasma levels in patients with moderate impairment. Transient, asymptomatic rises in transaminases, AST and ALT are common, especially early in treatment. Single case report of mild cholestatic liver injury that resolved on stopping treatment.16 Brexpiprazole7,17 Little information. Use no more than 3mg/day (schizophrenia) or 2mg/day (depression or agitation in Alzheimer's disease) in moderate or severe hepatic failure. Long half-life (~90 hours). Cariprazine7,18 Occasional, non-clinically relevant increases in ALT and AST. No dosage adjustment is required in patients with mild or moderate hepatic failure; not advised in severe hepatic disease (has not been evaluated). Long half-life (~2–4 days). Hepatitis has been reported. Clozapine1,6,7,19,20 Very sedative and constipating. Contraindicated in active liver disease (associated with nausea, anorexia or jaundice), progressive liver disease or hepatic failure. In less severe disease, start with 12.5mg and increase slowly, using plasma levels to gauge metabolising capacity and guide dosage adjustment. More frequently associated with changes in liver enzymes than other antipsychotics. Transient elevations in AST, ALT and GGT to over twice the normal range occur in up to a third of people, resolving spontaneously in 6–12 weeks.21 Clozapine-induced hepatitis, jaundice, cholestasis and liver failure have been reported. Clozapine should be discontinued if these develop. Successful rechallenge following hepatitis has been described.22,23 Flupentixol/ zuclopenthixol6,7,24,25 Both are extensively hepatically metabolised. Abnormal LFTs and (rarely) jaundice have been reported with flupentixol.6 Small, transient elevations in transaminases, cholestatic hepatitis and jaundice6 have been reported in some patients treated with zuclopenthixol. One report of flupentixol-induced hepatitis.26 No other literature reports of use or harm.27 Reduce doses by 50% in patients with compromised hepatic function. Depot preparations are best avoided, as altered pharmacokinetics will make dosage adjustment difficult and adverse effects from accumulation more likely. Haloperidol6 Extensively hepatically metabolised. Halve initial doses, adjust dose with smaller increments and at longer intervals. Transient and asymptomatic elevations in LFTs reported in 20% of patients.28 Isolated reports of cholestasis, acute hepatic failure, hepatitis and abnormal LFTs.6,7 Iloperidone7,11,29 Hepatically metabolised. Reduce dose in moderate impairment (twofold increase in active metabolites) and avoid completely in severe hepatic impairment (no studies done). No dose reduction necessary in mild impairment. Infrequent reports of cholelithiasis. Lumateperone30,31 Hepatically metabolised to active metabolites. No dose adjustment required in mild impairment. Increased exposure to lumateperone in moderate and severe impairment; manufacturer recommends dose of 21mg daily. Increases in transaminases reported in licensing trials. (Continued)

 CHAPTER 8 Table 8.1 (Continued) Drug Comments Lurasidone6,7,11 Hepatically metabolised. No dose adjustment is required in mild hepatic impairment. Manufacturer recommends a starting dose of 18.5mg (20mg) in moderate or

severe hepatic impairment, and a maximum dose of 74mg (80mg)/day in moderate impairment (1.7-fold increase in exposure) and of 37mg (40mg)/day in severe impairment (threefold increase in exposure). Increases in ALT reported infrequently. Olanzapine1,6,7,11 Although extensively hepatically metabolised, the pharmacokinetics of olanzapine seem to change little in severe hepatic impairment. It is sedative and anticholinergic (can cause constipation) so caution is advised. Start with 5mg/day in moderate or severe impairment and consider using plasma levels to guide dosage (aim for 20–40mcg/L). Dose-related, transient, asymptomatic elevations in ALT and AST are very common in physically healthy adults, particularly early in treatment. Along with clozapine, more often associated with drug-induced liver injury than other antipsychotics.32,33 Paliperidone6,7,11 Mainly excreted unchanged so no dosage adjustment required for mild to moderate impairment. May be a good choice for patients with pre-existing hepatic disease.34–37 However, no data are available with respect to severe hepatic impairment, so caution required. Rises in transaminases and GGT reported, and some cases of jaundice and hepatic steatosis.38 One case report of hepatotoxicity with risperidone that did not remit on switching to paliperidone – it is possible that paliperidone may cause hepatotoxicity.39 Phenothiazines6,7,32 All cause sedation and constipation. Transient abnormalities in LFTs reported. Associated with cholestasis and some reports of fulminant hepatic cirrhosis. Best avoided completely in hepatic impairment, some phenothiazines are actively contraindicated. Chlorpromazine is particularly hepatotoxic and is also associated with rare cases of immune-mediated obstructive jaundice which may progress to liver disease. Pimavanserin7 Active metabolite has a very long half-life (200 hours) but hepatic impairment does not appear to affect plasma concentrations. Manufacturer advises that no dose adjustment is required. No reports of hepatotoxicity. Quetiapine6,7,11,40 Extensively hepatically metabolised but short half-life. Clearance reduced by a mean of 30% in hepatic impairment so start at 25mg/day (IR preparation) or 50mg/day (XL preparation) and increase in 25–50mg/day increments. Can cause sedation and constipation. Transient rises in AST, ALT and GGT reported, as well as jaundice and hepatitis.41 Severe hepatic toxicity probably more common with quetiapine (1.65% of patients) than other SGAs.41 Several cases of fatal hepatic failure and of hepatocellular damage reported. A number of studies describe safe use in patients with alcohol dependence.42–44 Risperidone1,6,7,11 Extensively hepatically metabolised and highly protein bound. Those with severe impairment should start at 0.5mg bd and increase by 0.5mg bd at a maximum rate of weekly for doses above 1.5mg bd. Risperidone Consta can be started at 12.5mg, or 25mg every 2 weeks if 2mg daily oral dosing has been tolerated. Okedi should be started at 75mg, after confirming tolerability of 3mg oral risperidone. Perseris can be given at 90mg monthly if 3mg oral risperidone is tolerated, and Uzedy at 50mg monthly if 2mg oral is tolerated. Transient, asymptomatic elevations in LFTs, cholestatic hepatitis, jaundice and rare cases of hepatic failure have been reported. Cross-hepatotoxicity with paliperidone has been reported.39 Steatohepatitis may arise as a result of weight gain.45 Sulpiride6,7 Almost completely renally excreted with a low potential to cause sedation or constipation. Dosage reduction should not be required. Rises in hepatic enzymes are common. Isolated case reports of cholestatic jaundice and primary biliary cirrhosis. ALT, alanine aminotransferase; AST, aspartate aminotransferase; bd, twice a day; GGT, gamma-glutamyl transferase.

04 - Antidepressants in hepatic impairment2

Antidepressants in hepatic impairment2

Prescribing in hepatic and renal impairment CHAPTER 8 Antidepressants in hepatic impairment2 Of those treated with antidepressants, 0.5–3% develop asymptomatic mild elevation of hepatic transaminases.46 Onset is normally between several days and 6 months of treatment initiation and the elderly are more vulnerable.46 Frank, clinically significant liver damage however is rare and mostly idiosyncratic (unpredictable and not related to dose). Cross-toxicity within class has been described.46 Table 8.2 lists antidepressants commonly used in hepatic impairment. Table 8.2 Antidepressants in hepatic impairment. Drug Comments Agomelatine6,7,46–48 Liver injury including hepatic failure, liver enzyme increases more than 10 x ULN, and hepatitis reported, most commonly in first months of treatment. Contraindicated in hepatic impairment, including cirrhosis and active liver disease. Dose-related increase in transaminases reported; perform LFTs at baseline, 3, 6, 12 and 24 weeks during initiation and at each dose increase, and thereafter where clinically indicated. Stop treatment if transaminases rise more than 3 x ULN. Use cautiously where other risk factors for hepatic disease are present. Under current monitoring restrictions, risk of liver injury is no higher than for other antidepressants.49,50 Almost all reactions are reversible on stopping agomelatine.47 Brexanolone7,28 No dose adjustment required in hepatic impairment. Does not appear to be hepatotoxic, although experience is limited. Citalopram7,51,52 Hepatically metabolised and accumulates in chronic dosing. Dosage reduction required in renal impairment because of the extended half-life of citalopram in renal impairment which results in steady-state concentrations at a given dose to be about twice as high as those found in patients with normal renal function. Greater risk of QT interval prolongation because of higher drug exposure. Restrict the maximum daily dose to 20mg in hepatic impairment. Exercise caution due to the increased risk of bleeding seen with all SSRIs. Duloxetine6,7,53–57 Hepatically metabolised. Clearance markedly reduced even in mild impairment. Reports of hepatocellular injury (liver enzyme increases more than 10 x ULN) and, less commonly, jaundice. Hepatic failure, sometimes fatal, has been reported. Contraindicated in hepatic impairment. Escitalopram7,58,59 Hepatically metabolised and accumulates in chronic dosing. Longer half-life and 60% higher exposure in mild to moderate impairment. Initiate the dose at 5mg daily for the first 2 weeks, maximum dose 10mg daily. Careful dose titration in severe hepatic impairment. Be aware of increased risk of bleeding and QT prolongation. Fluoxetine6,7,60–64 Extensively hepatically metabolised with a long half-life (further

increased in hepatic insufficiency). Kinetic studies demonstrate accumulation in compensated cirrhosis. Dose reduction (of at least 50%) or alternate-day dosing is recommended. Attainment of steady state is delayed. Asymptomatic increases in LFTs found in 0.5% of healthy adults. Rare cases of hepatitis reported. Fluvoxamine7,28,65 Hepatically metabolised and accumulates in chronic dosing. Dose adjustments are necessary in hepatic impairment. Low risk of hepatotoxicity. Raised LFTs rarely reported and do not require dose change or fluvoxamine discontinuation. Be mindful of increased risk of bleeding. Levomilnacipran, milnacipran7,28 No dose adjustment required in hepatic impairment, although the manufacturers of milnacipran advise avoiding in chronic liver disease, alcohol use or severe hepatic dysfunction. Increased liver enzymes have been reported, and hepatitis with milnacipran. Discontinue use if jaundice or liver dysfunction occurs. (Continued)

758 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 8 Table 8.2 (Continued) Drug Comments MAOIs6,7,66 Rare cases of fatal hepatic necrosis, hepatotoxicity and jaundice with phenelzine. Rarely hepatitis is reported with tranylcypromine, and one isolated case of fatal hepatotoxicity with moclobemide. Doses of moclobemide should be reduced to half or one-third in hepatic impairment. Selegiline has not been associated with liver injury, although one study reported serum enzyme elevations in 41% of patients (other studies found no changes). Transdermal doses do not need to be adjusted in mild or moderate impairment (no data for severe impairment).67 Selegiline orodispersible tablets should be started at 1.25mg/day in mild to moderate impairment and are contraindicated in severe disease. Non-selective MAOIs are contraindicated in patients with hepatic impairment. Mirtazapine6,7,68 Hepatically metabolised and sedative. 50% dose reduction recommended based on kinetic data. Mild, asymptomatic increases in LFTs seen in healthy adults (ALT

> 3 times the upper limit of normal in 2%). Few cases of cholestatic and hepatocellular damage reported. Has been used safely in patients with primary biliary cholangitis.69 Paroxetine70–72 Hepatically metabolised and accumulates in chronic dosing. Dose adjustments are necessary in hepatic impairment. Raised LFTs and rare cases of hepatitis, with or without jaundice, including chronic active hepatitis, have been reported. Paroxetine has demonstrated mild to moderate antipruritic effects in cholestatic pruritus. Be aware of increased risk of bleeding. Reboxetine6,7,73 50% reduction in starting dose advised. Does not seem to be associated with hepatotoxicity. Sertraline7,28,72,74 Hepatically metabolised and accumulates in chronic dosing. Use a low or less frequent dose in mild hepatic impairment. Avoid in patients with moderate (Child–Pugh score 7–10) or severe hepatic impairment (Child–Pugh score 10–15). Rare instances of acute liver injury, with or without jaundice, have been described. Sertraline is used in the management of cholestatic pruritus. Be aware of increased risk of bleeding. Tricyclics6,7,75 All are hepatically metabolised, highly protein bound and will accumulate. They vary in their propensity to cause sedation and constipation. All are associated with raised LFTs and rare cases of hepatitis. Sedative TCAs such as trimipramine, imipramine, dothiepin (dosulepin) and amitriptyline are best avoided. Venlafaxine/ desvenlafaxine6,7,76,77 Dosage

reduction of 50% advised in mild and moderate hepatic impairment. Rare cases of hepatitis reported. Vilazodone7 No dose adjustment required in hepatic impairment. Does not appear to affect liver enzymes and no cases of hepatotoxicity, but data are limited, and all other SSRIs have been linked to liver toxicity. Vortioxetine6,78,79 Extensively metabolised in the liver. Little experience in hepatic impairment, but pharmacokinetic studies suggest no dose reduction is required. Does not seem to be associated with hepatotoxicity, but experience is limited and all other SSRIs are implicated in rare instances of liver toxicity. ALT, alanine aminotransferase; LFTs, liver function tests; MAOIs, monoamine oxidase inhibitors; TCAs, tricyclic antidepressants; ULN, upper limit of normal.

05 - Mood stabilisers in hepatic impairment6,7,80

Mood stabilisers in hepatic impairment6,7,80

Prescribing in hepatic and renal impairment CHAPTER 8 Mood stabilisers in hepatic impairment6,7,80 Recommendations for the use of mood-stabilising medications in hepatic impairment are summarised in Table 8.3. Table 8.3 Mood stabilisers in hepatic impairment. Drug Comments Carbamazepine6,7,80 Extensively hepatically metabolised and potent inducer of CYP450 enzymes (this can cause modest elevations in gamma-glutamyl transferase and alkaline phosphatase, which in themselves are not an indication for stopping6). In chronic stable disease, caution is advised. Associated with hepatitis, cholangitis, cholestatic and hepatocellular jaundice, and hepatic failure (rare). Adverse hepatic effects are most common in the first 2 months of treatment.80 Hepatocellular damage is often associated with a poor outcome. Vulnerability to carbamazepine-induced hepatic damage may be genetically determined.80 Avoid use in acute liver disease. In chronic liver disease reduce starting dose by 50%7 and titrate up slowly, using plasma levels to guide dosage. Stop if liver function tests (LFTs) deteriorate. Lamotrigine28 Manufacturers advise 50% reduction in initial dose, dose escalation and maintenance dose in moderate hepatic impairment and 75% reduction of these parameters in severe hepatic impairment. Discontinue if there is lamotrigine-induced rash (which can be serious). Elevated LFTs and hepatitis reported. Women, children and patients taking valproate appear to be at increased risk of lamotrigine-related hepatotoxicity. Lithium7 Not metabolised so dosage reduction not required as long as renal function is normal. Use serum levels to guide dosage and monitor more frequently if ascites status changes (volume of distribution will change). Asymptomatic and transient LFT abnormalities reported in small proportion of patients on long-term therapy.28 One case of ascites and one of hyperbilirubinaemia reported over many decades of lithium use worldwide. Valproate81 Highly protein bound and hepatically metabolised. Reduce doses and closely monitor LFTs in hepatic impairment. Use plasma levels (measure free levels; total concentrations may appear to be normal) to guide dosage. Contraindicated in severe and/or active hepatic impairment or family history of severe impairment. Impairment of usual metabolic pathway can lead to generation of hepatotoxic metabolites via alternative pathway. Risk of liver toxicity is increased in people with hepatic insufficiency if salicylates are used concomitantly. Associated with elevated LFTs and serious hepatotoxicity including fulminant hepatic failure (sometimes fatal). Mitochondrial disease, learning disability, polypharmacy, metabolic disorders and underlying hepatic disease may be risk

factors. Particularly hepatotoxic in very young children. The greatest risk is in the first 3 months of treatment.

06 - Stimulants in hepatic impairment[6,7,82]

Stimulants in hepatic impairment[6,7,82]

07 - Sedatives in hepatic impairment

Sedatives in hepatic impairment

760 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 8 Stimulants in hepatic impairment6,7,82 Recommendations for the use of stimulant medications in hepatic impairment are outlined in Table 8.4. Sedatives in hepatic impairment Table 8.5 summarises recommended sedatives in hepatic impairment. Table 8.5 Sedatives in hepatic impairment. Drug Comments Benzodiazepines Extensively hepatically metabolised. Prolonged duration of effect particularly for drugs with active metabolites (diazepam, midazolam, clonazepam). Lorazepam, oxazepam and temazepam do not have active metabolites and are preferred. Lorazepam is considered the best tolerated in advanced liver disease28 and is commonly used in alcohol withdrawal. Liver enzyme elevations are uncommon and liver injury very rare.28 Melatonin7,89 Complex handling of melatonin in liver impairment. Reduced clearance and prolonged half-life contribute to higher circulating levels of endogenous melatonin in daytime hours; negative feedback and accumulation of toxic products results in reduced endogenous production. Relevance to dosing of exogenous melatonin is unclear, although toxicity of melatonin is minimal. Manufacturer advises avoiding in moderate or severe liver disease. Rarely associated with changes in liver function tests (LFTs). Promethazine7 Extensive hepatic metabolism. Manufacturers advise caution in liver impairment. Jaundice reported with high doses. Despite widespread use, no reports of LFT abnormalities or toxicity with lower doses.28 Z drugs7,90,91 Hepatically metabolised, but all have a relatively short half-life. Reduce initial doses in mild to moderate impairment (use zopiclone 3.75mg, zolpidem 5mg, zaleplon 5mg). Avoid in severe impairment. Manufacturers warn that benzodiazepines as a class may precipitate encephalopathy. Zaleplon is subject to significant first-pass metabolism and zolpidem plasma concentrations and half-life are significantly increased in hepatic impairment. These agents should be used with caution.92 Although zopiclone has the longer half-life, this may not be clinically relevant except in severe disease.90 Zopiclone and zaleplon have not been associated with hepatotoxicity. There are rare reports of abnormal LFTs and a single case of liver injury with zolpidem.28 There is one case of acute liver injury with eszopiclone (a zopiclone isomer).93 Table 8.4 Stimulants in hepatic impairment. Drug Comments Atomoxetine83 Reduce initial and target dose by 50% in moderate impairment, and by 75% in severe impairment. Very rare reports of liver toxicity, manifested by elevated hepatic enzymes, and raised bilirubin with jaundice. Manufacturer states ‘discontinue in patients with jaundice or laboratory evidence of liver

injury, and do not restart’. Dexamfetamine/ lisdexamfetamine84,85 Little experience in liver disease. Manufacturers recommend cautious dose titration. Very rarely associated with abnormal liver function, two case reports of hepatotoxicity.86,87 Methylphenidate88 Mild and transient elevations in liver enzymes have been reported. Rare reports of liver dysfunction and hypersensitivity reactions. Limited experience in liver disease.

08 - Other psychotropics in hepatic impairment

Other psychotropics in hepatic impairment

09 - Summary of recommended psychotropics in hepat

Summary of recommended psychotropics in hepatic impairment

Prescribing in hepatic and renal impairment CHAPTER 8 Other psychotropics in hepatic impairment Table 8.6 gives a summary of other psychotropics recommended in hepatic impairment. Summary of recommended psychotropics in hepatic impairment Table 8.7 gives an outline of the drug groups of psychotropics recommended for use in hepatic impairment. Table 8.6 Other psychotropics in hepatic impairment. Drug Comments Bremelanotide7 No dose adjustment required in mild to moderate hepatic impairment. Use with caution in severe impairment; adverse effects more likely.30 One case of acute hepatitis reported. Deutetrabenazine6,28 Not studied in hepatic impairment but, based on experience with tetrabenazine, use is contraindicated. Limited information available but clinically relevant hepatotoxicity not reported. Occasional asymptomatic rises in ALT. Gabapentin Largely renally excreted but occasional cases of liver toxicity reported.94,95 Lemborexant, daridorexant, suvorexant7,30 No dose adjustments in mild or moderate impairment required for suvorexant. For lemorexant and daridorexant, no dose adjustment in mild impairment (risk of increased somnolence). In moderate impairment, starting and maximum dose of 5mg for lemborexant, 25mg for daridorexant. None is recommended in severe impairment. Little experience but hepatotoxicity not reported.96 Pitolisant6,30 Extensively hepatically metabolised. No dose adjustment in mild impairment. In moderate impairment the half-life is doubled; daily dose can be increased 2 weeks after initiation, daily maximum 17.8mg. Manufacturers recommend monitoring patients with hepatic impairment for increased QTc. Contraindicated in severe impairment. Hepatic enzyme increases are uncommon. No reports of liver injury. Pregabalin Not metabolised and largely renally excreted.97 Rare cases of hepatoxicity.98,99 Solriamfetol6 Not metabolised. No known problems in liver impairment, no reports of liver injury. Valbenazine7,28 Hepatically metabolised pro-drug of α--

dihydrotetrabenazine. Unlike deutetrabenazine, valbenazine is not contraindicated in liver disease, but maximum dose of 40mg in moderate to severe impairment. Few data, but no reports of clinically relevant liver injury other than a single report of reactivation of pre-existing hepatitis C. ALT, alanine aminotransferase. Table 8.7 Psychotropic drug groups in hepatic impairment. Drug group Recommended drugs Antipsychotics Sulpiride/amisulpride: no dosage reduction required if renal function is normal Paliperidone: if depot required. Antidepressants Paroxetine, sertraline, citalopram, escitalopram or vortioxetine: start at low dose. Titrate slowly (if required) as above. Mood stabilisers Lithium: use plasma levels to guide dosage. Care needed if ascites status changes. Sedatives Lorazepam, oxazepam, temazepam: short half-life with no active metabolites. Use low doses with caution, as sedative drugs used in severe disease can precipitate hepatic encephalopathy. Zopiclone: 3.75mg with care in moderate hepatic impairment.

10 - Drug induced hepatic damage

Drug-induced hepatic damage

762 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 8 Drug-induced hepatic damage Hy's rule is defined as alanine aminotransferase (ALT) more than three times the upper limit of normal combined with serum bilirubin more than two times the upper limit of normal. This is recommended by the US Food and Drug Administration (FDA) to assess the hepatotoxicity of new drugs.80 Drug-induced hepatic damage can be due to: ■ ■Direct dose-related hepatotoxicity (type 1 adverse drug reaction). A small number of drugs fall into this category (e.g. paracetamol, alcohol). ■ ■Hypersensitivity reactions (type 2 adverse drug reaction). These can present with rash, fever and eosinophilia. Almost all drugs have been associated with cases of hepatotoxicity; the frequency varies. Almost any type of liver damage can occur, ranging from mild transient asymptomatic increases in LFTs to fulminant hepatic failure. See Tables 8.1–8.6 for details of the hepatotoxic potential of individual drugs. Risk factors for drug-induced hepatotoxicity include:100 ■ ■Increasing age. ■ ■Female gender. ■ ■Alcohol consumption. ■ ■Co-prescription of enzyme--inducing drugs. ■ ■Genetic predisposition. ■ ■Obesity. ■ ■Pre-existing liver disease (small effect). When interpreting LFTs, remember that:101 ■ ■About 12% of the healthy adult population have one LFT outside (above or below) the normal reference range. ■ ■Up to 10% of patients with clinically significant hepatic disease have normal LFTs. ■ ■Individual LFTs lack specificity for the liver, but more than one abnormal test greatly increases the likelihood of liver pathology. ■ ■The absolute values of LFTs are a poor indicator of disease severity. When monitoring LFTs consider the following: ■ ■Ideally LFTs should be measured before treatment starts so that 'baseline' values are available. ■ ■LFT elevations of over two times the upper limit of the normal reference range are rarely clinically significant. ■ ■Most drug-related LFT elevations occur early in treatment (first month) and are transient. They may indicate adaptation of the liver to the drug rather than damage per se. Transient LFT elevations may also occur during periods of weight gain.102 ■ ■If LFTs are persistently elevated more than threefold, continuing to rise or accompanied by clinical symptoms, the suspected drugs should be withdrawn. ■ ■When tracking change, >20% change in liver enzymes is required to exclude bio logical or analytical variation.

11 - References

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Prescribing in hepatic and renal impairment CHAPTER 8 References

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12 - Renal impairment

Renal impairment

13 - General principles of prescribing in renal im

General principles of prescribing in renal impairment

766 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 8 Renal impairment Using drugs in patients with renal impairment needs careful consideration. This is partly because some drugs are nephrotoxic but principally because the pharmacokinetics (absorption, distribution, metabolism, excretion) of drugs are altered in renal impairment. In particular, patients with renal impairment have a reduced capacity to excrete drugs and their metabolites. General principles of prescribing in renal impairment ■ ■Estimate the excretory capacity of the kidney. Laboratories usually report renal function based on the estimated glomerular filtration rate (eGFR). This is derived from either the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula or the Modification of Diet in Renal Disease (MDRD) formula. The CKD-EPI formula is more accurate than the MDRD and is preferred, but note that these estimates are still less than perfect when compared with directly measured GFR.1 ■ ■Check proteinuria by measuring urinary albumin and calculate the albumin : creatinine ratio. This is because proteinuria is a significant risk factor for progression to end stage disease.1 ■ ■For most drugs and most adult patients of average build and height, eGFR (calculated using the CKD-EPI formula, Box 8.1) can be used to determine dose adjustments. ■ ■For nephrotoxic drugs, elderly patients (75 years and over) and patients at both extremes of muscle mass (body mass index [BMI] <18 or >40kg/m2), calculate creatinine clearance (CrCl) to determine dose adjustments. In addition, the Medicines Healthcare products Regulatory Agency (MHRA) advises that CrCl should be used as an estimate of renal function for direct-acting oral anticoagulants (DOACs) and drugs with a narrow therapeutic index that are mainly renally excreted (e.g. lithium) (UK Kidney Association, https://ukkidney.org). The Cockroft and Gault equation should be used to calculate CrCl (Box 8.2). Box 8.1 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula This replaces the previously used modification of diet in renal disease (MDRD) equation)2 although some pathology departments still use MDRD. GFR S k,1 S k,1 0.993 1.018 if cr cr 1.209 Age

min ( ) max [( ) / /

female 1.159 if black] [ ]

Where Scr is serum creatinine in mg/dL κ is 0.7 for females and 0.9 for males α is -0.329 for females and -0.411 for males min indicates the minimum of Scr/κ or 1 max indicates the maximum of Scr/κ or 1 ■ ■Online calculator available at https://www.kidney.org/professionals/kdoqi/gfr_calculator

14 - Stage of renal impairment

Stage of renal impairment

Prescribing in hepatic and renal impairment CHAPTER 8 Stage of renal impairment Figure 8.1 indicates how to classify the stage of renal impairment.2 Box 8.2 Cockroft and Gault equation* CrCl ml/ F age in years ideal body weight kg Ser (min) (( )) ( ) um creatinine mol/L ( )

Where F = 1.23 (men) and 1.04 (women) Ideal body weight should be used for patients at extremes of body weight or else the result of the calculation is a poor estimate For men, ideal body weight (kg) = 50kg + 2.3kg per inch over 5 feet For women, ideal body weight (kg) = 45.5kg + 2.3kg per inch over 5 feet ■ ■Online calculator available at https://www.nuh.nhs.uk/staff--area/antibiotics/creatinine-clearance- calculator * This equation is not accurate if plasma creatinine is unstable (e.g. acute renal failure), in obesity, in pregnant women, in children or in diseases causing the production of abnormal amounts of creatinine. It has only been validated in white patients. Creatinine clearance is not the same as GFR and is relatively less representative of GFR in severe renal failure. ACR categories (mg/mmol) Description and range GFR categories (mL/min/1.73m2) Description and range A1 A2 A3 Normal to mildly increased Moderately increased Severely increased <3 ≥90 60–89 45–59 30–44 15–29 <15 Normal and high Mild reduction related to normal range for a young adult Mild–moderate reduction Moderate–severe reduction Severe reduction Kidney failure G1 G2 G3a G3b G4 G5 No CKD in the absence of markers of kidney damage Refer for specialist assessment 3–30 Refer for specialist assessment if the person has: • a sustained decrease in GFR of 25% or more and a change in GFR category or sustained decrease in GFR of 15 mL/min/1.73 m2 or more within 12 months • hypertension that remains poorly controlled despite the use of at least 4 antihypertensive drugs at therapeutic doses (see also ‘Hypertension’ NICE clinical guideline 127) • known or suspected rare or genetic causes of CKD • suspected renal artery stenosis Refer for specialist assessment if the person has any of the criteria in A2, or: • ACR 70mg/mmol or more, unless known to be caused by diabetes and already appropriately treated • haematuria Manage in primary care according to recommendations

> 30 Figure 8.1 Classification of renal impairment. ACR, albumin : creatinine ratio; CKD, chronic kidney disease; GFR, glomerular filtration rate.

15 - Notes

Notes

768 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 8 Notes ■ ■Monitor decline in renal function over a considerable period as a 30% change over 2 years is associated with a fivefold increase in risk of end stage renal disease. Chronic kidney disease (CKD) progression is often non-linear.1 ■ ■Monitor risk of moving from CKD stage 3–5 (eGFR 10–59) to dialysis/-transplantation using the Tangri score at https://qxmd.com/calculate/calculator_125/kidney-failure-risk-equation-8-variable. The four (age, sex, eGFR, urine albumin : creatinine ratio) and eight (previous four items plus serum calcium, phosphorus, bicarbonate, albumin) variable equations accurately predict the 2- and 5-year probability of treated kidney failure (dialysis or transplantation) for a potential patient with CKD stage 3–5.3 ■ ■In general, renal function significantly affects overall drug elimination so the amount of drug excreted unchanged in urine should be 30% or more of the dose.4 ■ ■Older adults (>65 years) should be assumed to have at least mild renal impairment. Their serum creatinine may not be raised because they have a smaller muscle mass. ■ ■Avoid drugs that are nephrotoxic (e.g. lithium, non-steroidal anti-inflammatory drugs) where renal reserve is limited. ■ ■Be cautious when using drugs that are extensively renally cleared (e.g. sulpiride, amisulpride, lithium). ■ ■Elimination of drugs metabolised hepatically can be reduced in kidney disease possibly by inhibition of enzymatic activity caused by uraemia.5 ■ ■Start at a low dose and increase slowly because, in renal impairment, the half-life of a drug and the time for it to reach steady state (amount absorbed is the same as cleared when the drug is given continuously) are often prolonged. Plasma level monitoring may be useful for some drugs. ■ ■Try to avoid long-acting drugs (e.g. depot preparations). Their dose and frequency cannot be easily adjusted should renal function change. ■ ■Prescribe as few drugs as possible. Patients with renal failure take many medications requiring regular review. Interactions and adverse effects can be avoided if fewer drugs are used. ■ ■Monitor patient for adverse effects. Patients with renal impairment are more likely to experience adverse effects and they may take longer to develop than in healthy patients. Adverse effects such as sedation, confusion and postural hypotension can be more common. ■ ■Be cautious when using drugs with anticholinergic effects, since they may cause urinary retention. ■ ■There are few clinical studies of the use of psychotropic drugs in people with renal impairment. Advice about drug use in renal impairment is often based on knowledge of the drug’s pharmacokinetics in healthy patients. ■ ■The effect of renal replacement therapies (e.g. dialysis) on drugs is difficult to predict. See Tables 8.8–8.14. Seek specialist advice. ■ ■Try to avoid drugs known to prolong the QTc interval. In established renal failure electrolyte changes are common so it is probably best to avoid antipsychotics with the greatest risk of QTc prolongation (see section on ECG changes – QT prolongation in Chapter 1). ■ ■Monitor weight carefully. Weight gain predisposes to diabetes which can contribute to rhabdomyolysis6 and renal failure. Psychotropic medications commonly cause weight gain.

Prescribing in hepatic and renal impairment CHAPTER 8 ■ ■Be vigilant for serotonin syndrome with antidepressants, dystonias and neuroleptic malignant syndrome (NMS) with antipsychotics. The resulting rhabdomyolysis can cause renal failure. There are case reports of rhabdomyolysis occurring with antipsychotics without other symptoms of NMS.7–9 ■ ■Depression is common in CKD but evidence for effectiveness of antidepressants in this condition is lacking.10,11 In CKD starting some antidepressants at a higher versus lower dose reduces mortality risk.12 Depression is poorly treated in patients on haemodialysis.13 In common with other chronic physical illnesses, depression in end stage renal disease may be associated with increased mortality,14–16 and the degree of risk may be linked to the severity of the depression.17 Non-drug treatment such as cognitive behavioural therapy, exercise or relaxation techniques probably reduces depressive symptoms for adults on dialysis.18 SSRIs are associated with hip fracture in patients on haemodialysis (adjusted odds ratio 1.25; 95% confidence interval [CI] 1.17, 1.35).19 ■ ■Both schizophrenia and bipolar disorder are associated with an increased risk of CKD.20,21 ■ ■Antipsychotics (e.g. olanzapine, quetiapine) may be associated with acute kidney injury22 possibly via their effects on blood pressure and urinary retention but studies are conflicting.23 ■ ■Mood-stabilising anticonvulsants used in bipolar disorder are associated with an increased rate of CKD.21 Table 8.8 Antipsychotic medications in renal impairment. Drug Comments Amisulpride24–27 Primarily renally excreted. 50% excreted unchanged in urine. Limited experience in renal disease, one study in Chinese patients showing more than twofold increase in AUC, trough and peak plasma concentrations with GFR 30mL/min.28 Manufacturer states no data with doses of >50mg but recommends following dosing: 50% of dose if GFR 30–60mL/min; 33% of dose if GFR is 10–30mL/min; no recommendations for GFR <10mL/min so best avoided in established renal failure. Aripiprazole24,25,27,29–32 Less than 1% of unchanged aripiprazole renally excreted. Manufacturer states no dose adjustment required in renal failure as pharmacokinetics are similar in healthy and severely renally diseased patients. There is one case report of safe use of oral aripiprazole 5mg in an 83-year-old man having haemodialysis. Avoid depot formulation where possible although there is a case report of aripiprazole 400mg depot use in a 64-year-old man on haemodialysis. Asenapine25,27,33 Extensively hepatically metabolised. Manufacturer states no dose adjustment required for patients with renal impairment but no experience with use if GFR <15mL/min. A 5mg single-dose study suggests that no dose adjustment is needed with any degree of renal impairment. Chlorpromazine24,27,34–36 Less than 1% excreted unchanged in urine. Caution required in severe impairment because of the risk of accumulation. No dose adjustment required for GFR >10mL/ min. For GFR <10mL/min, start with small doses and monitor for anticholinergic, sedative and hypotensive adverse effects. (Continued)

770 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 8 Table 8.8 (Continued) Drug Comments Clozapine25,27,37–41 Contraindicated by manufacturer in severe renal disease, but only trace amounts of unchanged clozapine are excreted in urine. No dose adjustment required in GFR

> 10mL/min, titrate cautiously in very severe impairment. Nocturnal enuresis and urinary retention are common adverse effects. Anticholinergic, sedative and hypotensive adverse effects are more frequent in patients with renal disease. May cause and aggravate diabetes, a common cause of renal disease. Rare case

reports of interstitial nephritis and acute renal failure, but also successful continuation after renal transplantation.42 Flupentixol24,25,27 Negligible renal excretion of unchanged flupentixol. Dosing: GFR 10–50mL/min dose as in normal renal function; GFR <10mL/min start with quarter to half of normal dose and titrate slowly. May cause hypotension and sedation in renal impairment and can accumulate. Manufacturer advises caution in renal failure because of increased cerebral sensitivity to antipsychotics. Avoid depot preparations in renal impairment. Haloperidol8,24,25,27,43,44 Less than 1% excreted unchanged in the urine. Manufacturer advises caution in renal failure. Dosing: GFR 10–50mL/min dose as in normal renal function; GFR <10mL/min start with a lower dose as can accumulate with repeated dosing. A case report of haloperidol use in renal failure suggests starting at a low dose and increasing slowly. Has been used to treat uraemia-associated nausea in renal failure. Avoid depot preparations in renal impairment. Lumateperone45,46 <1% excreted unchanged in urine. Manufacturer advises no dose adjustment needed in renal impairment. Lurasidone24 9% excreted unchanged in the urine. Serum concentrations are increased by 1.5-, 1.9- and 2.0-fold in mild, moderate and severe impairment, respectively. Manufacturer advises a starting dose of 18.75mg (20mg) and maximum dose of 74mg (80mg) per day if GFR <50mL/min. Avoid in GFR <15mL/min unless benefits outweigh risks (no data to support use). Renal failure has been reported rarely. Olanzapine7,25,27,34,44,47 57% of olanzapine is excreted mainly as metabolites (7% excreted unchanged) in urine. Dosing: UK manufacturers recommend GFR <50mL/min initially 5mg daily and titrate as necessary. Avoid long-acting preparations in renal impairment unless the oral dose is well tolerated and effective. UK manufacturer recommends a lower long--acting injection starting dose of 150mg, 4-weekly in patients with renal impairment. US manufacturers state that no dose adjustment is required for oral or depot preparation. May cause and aggravate diabetes, a common cause of renal disease. Hypothermia has been reported when used in renal failure. Paliperidone25,27,34 Paliperidone is a metabolite of risperidone. 59% excreted unchanged in urine. Dosing: GFR 50–80mL/min, 3mg daily and increase according to response to max. of 6mg daily; GFR 10–50mL/min, 3mg alternate days (or 1.5mg daily) increasing to 3mg daily according to response. Use with caution as clearance is reduced by 71% in severe kidney disease. Manufacturer contraindicates oral form if GFR <10mL/min due to lack of experience, and monthly, 3-monthly and 6-monthly depot preparations if GFR <50mL/min (reduced loading and maintenance doses if GFR >50mL/min). Two case reports of successful paliperidone monthly injection use in patients with renal failure undergoing haemodialysis.48,49

Prescribing in hepatic and renal impairment CHAPTER 8 Drug Comments Pimavanserin45,50 <1% excreted unchanged in urine. Manufacturer states no dose adjustment needed in GFR ≥30mL/min but advises to avoid if GFR <30mL/min due to lack of data. Pimozide24,25,27 <1% of pimozide excreted unchanged in the urine; dose reductions not usually needed in renal impairment. Dosing:

GFR 10–50mL/min dose as in normal renal function; GFR <10mL/min start at a low dose and increase according to response. Manufacturer cautions in renal failure. Quetiapine24,25,27,51–53 <5% of quetiapine excreted unchanged in the urine. Plasma clearance reduced by an average of 25% in patients with a GFR <30mL/min but manufacturer states no dose adjustment is necessary. Case reports (thrombotic thrombocytopenic purpura, DRESS and non-NMS rhabdomyolysis) resulting in acute renal failure with quetiapine have been published. Risperidone24,25,27,44,54–57 Clearance of risperidone and the active metabolite of risperidone (9-OH-) is reduced by 60% in patients with moderate to severe renal disease. Dosing: GFR <50mL/min 0.5mg twice daily for at least 1 week then increasing by 0.5mg twice daily to 1–2mg bd. The long-acting injection should only be used after titration with oral risperidone as described above. If 2mg orally is tolerated, 25mg intramuscularly every 2 weeks (Risperdal Consta®) can be administered. Manufacturers of the Okedi® monthly injection do not recommend use in GFR <60mL/min. Risvan® 75mg monthly or PerserisTM (subcutaneous) 90mg monthly can be used if 3mg oral is tolerated. UzedyTM can be given 50mg monthly if 2mg oral is tolerated. There are two case reports of successful use of risperidone long-acting injection in haemodialysis at a dose of 50mg 2 weekly in one patient and 37.5mg then 25mg in an older adult. Another describes the successful use of risperidone in a child with steroid-induced psychosis and nephrotic syndrome. Sulpiride6,24,25,27,58 Almost totally renally excreted, with 95% excreted in urine and faeces as unchanged sulpiride. Dosing regimen: GFR 30–60mL/min give 70% of normal dose; GFR 10–30mL/min give 50% of normal dose; GFR <10mL/min give 34% of normal dose. Alternately, the dosing interval can be prolonged by a factor of 1.5, 2 and 3, respectively. There is a case report of renal failure with sulpiride due to diabetic coma and rhabdomyolysis. Probably best avoided in renal impairment. Trifluoperazine27 Less than 1% excreted unchanged in the urine. Dose GFR <10–50mL/min as for normal renal function – start with a low dose. Very limited data. Ziprasidone24,44,59,60 <1% renally excreted unchanged. No dose adjustment needed for GFR >10mL/min but care needed with using the injection as it contains a renally eliminated excipient (cyclodextrin sodium). Case report of 80mg twice daily dose used in a patient on haemodialysis who then developed agranulocytosis.61 Zuclopenthixol24,27 10–20% of unchanged drug and metabolites excreted unchanged in urine. Manufacturer cautions use in renal disease as can accumulate. Dosing: 10–50mL/min dose as in normal renal function; GFR <10mL/min start with 50% of the dose and titrate slowly. Avoid both intramuscular preparations (acetate and decanoate) in renal impairment. If use is essential, follow the same dosing guidance as for oral. AUC, area under the curve; bd, twice a day; DRESS, drug reaction with eosinophilia and systemic symptoms; GFR, glomerular filtration rate. Table 8.8 (Continued)

 Table 8.9 Antidepressants in renal impairment.10 Drug Comments Agomelatine25 Negligible renal excretion of unchanged agomelatine. No data on use in renal disease. Manufacturer says pharmacokinetics unchanged in small study of 25mg dose in severe renal impairment but cautions use in moderate or severe renal disease. A growing number of studies demonstrate nephroprotective effects in rats. Amitriptyline24,25,27,36,44,62–64 <2% excreted unchanged in urine; no dose adjustment needed in renal failure. Dose as in normal renal function but start at a low dose and increase slowly. Monitor patient for urinary retention, confusion, sedation and postural hypotension. Has been used to treat pain in those with renal disease. Associated with acute kidney injury.64 Brexanolone45,65 <1% excreted unchanged in urine. Manufacturer states no dosage adjustment is recommended in patients with GFR 15–60mL/min; avoid use in patients with GFR of <15mL/min because of the potential accumulation of the injection solubilising agent, betadex sulfobutyl ether sodium.

Bupropion24,25,27,36,44,66–68 (amfebutamone) 0.5% excreted unchanged in urine but in patients with renal impairment, plasma concentrations are higher, elimination half-life is longer and oral clearance is significantly lower. Metabolites may accumulate, increasing the risk of seizures. In renal impairment, reduce dose to 150mg once daily and/or reduce frequency of dosing. A single-dose study in haemodialysis patients (stage 5 disease) recommended a dose of 150mg every 3 days. Has been used to treat sexual dysfunction in mild to moderately depressed patients with chronic kidney disease. Citalopram24,25,27,44,69–75 <13% of citalopram excreted unchanged in urine. Single-dose studies in mild and moderate renal impairment show no change in the pharmacokinetics of citalopram. Dosing is as for normal renal function; however, use with caution if GFR <10mL/min due to reduced clearance. The manufacturer does not advise use if GFR <20mL/min. Renal failure has been reported with citalopram overdose. Citalopram can treat depression in chronic renal failure and improve quality of life but use of citalopram (or escitalopram) is associated with a higher risk of sudden cardiac death vs other SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline) when used in patients on haemodialysis (adjusted hazard ratio 1.18; 95%CI 1.05, 1.31). Concurrent PPI use may increase the risk in haemodialysis;76 minimising the serum-to-dialystate potassium gradient may attenuate it.77 A case report of hyponatraemia has been reported in a renal transplant patient on citalopram. Clomipramine25,27,34,36,78 2% of unchanged clomipramine excreted in urine. Dosing: GFR 20–50mL/min dose as for normal renal function; GFR <20mL/min, effects unknown, start at a low dose and monitor patient for urinary retention, confusion, sedation and postural hypotension as accumulation can occur. There is a case report of clomipramine- induced interstitial nephritis and reversible acute renal failure. Desvenlafaxine10,34,79,80 45% of desvenlafaxine excreted unchanged in urine. Manufacturer recommends GFR 30–50mL/min 50mg/day; GFR <30mL/min 25mg/day or 50mg on alternate days. Half-life is prolonged and desvenlafaxine accumulates as GFR decreases. Urinary retention, delay when starting to pass urine and proteinuria have been reported as adverse effects. Dosulepin27,34,81 (dothiepin) 56% of mainly active metabolites renally excreted. They have a long half-life and may accumulate, resulting in excessive sedation. Dosing: GFR 20–50mL/min dose as for normal renal function; GFR <20mL/min start with a small dose and titrate to response. Monitor patient for urinary retention, confusion, sedation and postural hypotension. Doxepin25,27,34,36,82 <1% excreted unchanged in urine. Dosing: GFR 10–50mL/min as in normal renal function but monitor patient for urinary retention, confusion, sedation and postural hypotension; GFR <10mL/min start with a small dose and increase slowly. Manufacturer advises using with caution. Haemolytic anaemia with renal failure has been reported with doxepin. Used topically to treat pruritis in chronic renal failure.

Prescribing in hepatic and renal impairment CHAPTER 8 Drug Comments Duloxetine27,34,83–85 <1% excreted unchanged in urine. Manufacturer states no dose adjustment is necessary for GFR >30mL/min; however, starting at a low dose and increasing slowly are advised. Duloxetine is contraindicated in patients with a GFR <30mL/min as it can accumulate in chronic kidney disease. Two case reports of acute renal failure with duloxetine have been reported. Serotonin syndrome was reported in a patient with chronic kidney disease on trazodone and duloxetine.86 Escitalopram27,34,75,87–89 8% excreted unchanged in urine. The manufacturer states dosage adjustment is not necessary in patients with mild or moderate renal impairment, but caution is advised if GFR <30mL/min so start with a low dose and increase slowly. A case study of reversible renal tubular defects and another of renal failure have been reported with escitalopram. One study says effective vs placebo in end stage renal disease. Use of escitalopram (or citalopram) is

associated with a higher risk of sudden cardiac death vs other SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline) when used in patients on haemodialysis (adjusted hazard ratio 1.18; 95%CI 1.05, 1.31). Concurrent PPI use may increase the risk in haemodialysis;76 minimising the serum-to-dialystate potassium gradient may attenuate it.77 Fluoxetine11,25,27,34,36,44,90–93 2.5–5% of fluoxetine and 10% of the active metabolite norfluoxetine are excreted unchanged in urine. Dosing: GFR 20–50mL/min dose as normal renal function; GFR <20mL/min consider using a low dose or on alternate days and increase according to response. Plasma levels after 2 months' treatment with 20mg (in patients on dialysis with GFR <10mL/min) are similar to those with normal renal function. Efficacy studies of fluoxetine in depression and renal disease are conflicting. One small placebo--controlled study of fluoxetine in patients on chronic dialysis found no significant differences in depression scores between the two groups after 8 weeks of treatment. Another found fluoxetine effective. A case series (n = 4) of once-weekly fluoxetine 90mg or 180mg use in depressed patients on haemodialysis describes efficacious use with better tolerability at 90mg dose. Fluvoxamine27,34,36,44,94 2% excreted unchanged in urine. Renal impairment does not appear to affect the pharmacokinetics of fluvoxamine, but the UK manufacturer recommends starting at a low dose. Acute renal failure has been reported. Variations in albumin levels might affect serum concentrations of fluvoxamine in haemodialysis. Imipramine25,27,34,36,62 <5% excreted unchanged in urine. No specific dose adjustment necessary in renal impairment. Monitor patient for urinary retention, confusion, sedation and postural hypotension. Renal impairment with imipramine has been reported and manufacturer advises caution in severe renal impairment. Renal damage reported rarely. Lofepramine25,27,34,95 There is little information about the use of lofepramine in renal impairment. <5% excreted unchanged in urine. Dosing: GFR 10–50mL/min dose as in normal renal function; GFR <10mL/min start with a small dose and titrate slowly. Manufacturer contraindicates in severe renal impairment. Mirtazapine25,27,34,96 75% excreted unchanged in urine. Clearance is reduced by 30% in patients with GFR of 11–39mL/min and by 50% in patients with GFR <10mL/min. Dosing advice: GFR 10–40mL/min dose as for normal renal function but monitor for adverse effects; GFR <10mL/min start at a low dose and monitor closely. Mirtazapine has been used to treat pruritis caused by renal failure97 and appetite loss in chronic kidney disease.98,99 Rarely associated with kidney calculus formation. Moclobemide25,27,34,100,101 <1% of parent drug excreted unchanged in urine; an active metabolite was found to be raised in patients with renal impairment but this does not appear to be clinically significant. Dose adjustments are not required in renal impairment. Table 8.9 (Continued) (Continued)

Nortriptyline27,34,36,44,62,102 <5% excreted unchanged in urine. If GFR 10–50mL/min dose as in normal renal function; if GFR <10mL/min start at a low dose. Plasma level monitoring recommended at doses of >100mg/day, as plasma concentrations of active metabolites are raised in renal impairment. Worsening of GFR in elderly patients has also been reported. Paroxetine25,27,34,36,103–106 <2% of oral dose excreted unchanged in urine. Single-dose studies show increased plasma concentrations of paroxetine when GFR <30mL/min. Dosing advice differs: GFR 30–50mL/min dose as normal renal function; GFR <10–30mL/min start at 10mg/ day (other source says start at 20mg) and increase dose according to response in 10mg increments/week, max. dose 40mg/day. Extended release paroxetine should be started at 12.5mg/day in severe renal impairment, max. dose 50mg/day in depression or panic disorder, 37.5mg/day in social anxiety disorder. Paroxetine 10mg daily has been used to treat depression in patients on haemodialysis. Rarely associated with Fanconi syndrome and acute renal failure. Phenelzine27,34 Approximately

1% excreted unchanged in urine. No dose adjustment required in renal failure. Reboxetine25,27,34,107,108 Approximately 10% of unchanged drug excreted unchanged in urine. Dosing: GFR <80mL/min, 2mg twice daily, adjusting dose according to response. Half-life is prolonged and plasma concentration increased as renal function decreases. Sertraline25,27,34,36,109–113 <0.2% of unchanged sertraline excreted in urine. Pharmacokinetics in renal impairment are unchanged in single-dose studies but no published data on multiple dosing. Dosing is as for normal renal function. Sertraline has been used to treat dialysis-associated hypotension114 and uraemic pruritis;115 however acute renal failure has been reported so it should be used with caution. Overall, studies of sertraline in patients with depression and chronic kidney disease fail to show efficacy. The CAST study, an RCT of sertraline (median dose 150mg) vs placebo in chronic non-dialysis- dependent kidney disease, found no difference in change in depressive symptoms.113 The ASCEND trial of sertraline vs CBT in patients on haemodialysis with depression found no significant differences between sertraline (to 200mg) and CBT in response and remission rates but QIDS-C depression scores at 12 weeks were lower for sertraline than CBT.116 Another small RCT (ASSertID study) in patients with depression on haemodialysis reported no difference between sertraline and placebo.117 Has been associated with serotonin syndrome when used in patents on haemodialysis. Case report of neutropenia when used in end stage renal disease.118 May reduce CRP in patients on haemodialysis with depression119 and a high CRP may predict response to sertraline (not placebo) in depression with chronic kidney disease.120 Trazodone25,27,34,121 <5% excreted unchanged in urine but care needed as approximately 70% of active metabolite also excreted. Dosing: GFR 20–50mL/min dose as normal renal function; GFR <20mL/min start with small dose and increase gradually; serotonin syndrome reported in a patient with chronic kidney disease on trazodone and duloxetine.86 Has been trialled (unsuccessfully) for insomnia in haemodialysis, incidence of adverse events was higher with trazodone vs placebo.122 Long-term use may be associated with an increased risk of chronic kidney disease.123 Trimipramine27,34,36,62,124,125 No dose reduction required in renal impairment; however, elevated urea, acute renal failure and interstitial nephritis have been reported. As with all tricyclic antidepressants in renal impairment, monitor patient for urinary retention, confusion, sedation and postural hypotension. Table 8.9 (Continued)

Prescribing in hepatic and renal impairment CHAPTER 8 Drug Comments Venlafaxine25,34,36,126–128 1–10% excreted unchanged in urine (30% as the active metabolite). Clearance is decreased and half-life prolonged in renal impairment. Dosing: GFR 30–90mL/min reduce by 25–50%; GFR <30mL/min reduce dose by at least 50%, consider alternate day dosing. Rhabdomyolyisis129 and renal failure have been reported rarely with venlafaxine. Has been used to treat peripheral diabetic neuropathy in haemodialysis patients. High doses may cause hypertension. Vortioxetine25,130 Negligible amounts are excreted unchanged in urine. Manufacturer advises that no dose adjustment is needed in renal impairment and end stage disease but advises caution due to a lack of data. CBT, cognitive behavioural therapy; CRP, C--reactive protein; GFR, glomerular filtration rate; PPIs, proton pump inhibitors. Table 8.9 (Continued) Table 8.10 Mood stabilisers in renal impairment. Drug Comments Carbamazepine25,27,34,131–134 2–3% of dose excreted unchanged in urine. Dose reduction not necessary in renal disease, although cases of renal failure, tubular necrosis and tubulointerstitial nephritis have been reported rarely and metabolites may accumulate. Can cause Stevens–Johnson syndrome and toxic epidermal necrolysis, which may result in acute renal failure. Maintenance therapy in bipolar disorder is associated with an increased rate of chronic kidney disease.21

Lamotrigine25,27,34,135–139 <10% of lamotrigine excreted unchanged in urine. Single-dose studies in renal failure show pharmacokinetics are little affected; however, inactive metabolites can accumulate (effects unknown) and half-life can be prolonged. Renal failure and interstitial nephritis have also been reported. Dosing: GFR <10–50mL/min use cautiously, start with a low dose, increase slowly and monitor closely. One source suggests in GFR <10mL/min use 100mg every other day. Lithium25,27,34,36,140,141 Lithium is nephrotoxic and contraindicated in severe renal impairment; 95% excreted unchanged in urine. Long-term treatment may result in impaired renal function in about a quarter of patients142 ('creatinine creep'), permanent changes in kidney histology, microcysts, oncocytoma and collecting duct renal carcinoma, nephrogenic diabetes insipidus, nephrotic syndrome and both reversible and irreversible kidney damage.143,144 However shorter studies in younger populations do not show declining GFR145 or the development of end stage renal disease.21,146,147 These differences may be due to methodology, improved monitoring and targeting recommended maintenance serum levels (0.6–0.8mmol/L in BPAD). Prevent nephrotoxicity by using once daily dosing, tightly adhering to recommended plasma levels, avoiding intoxication, assertively treating comorbidities and actively monitoring kidney function. Collaboration is vital between psychiatrist, nephrologist and patient in decision-making if chronic kidney disease occurs.148 Risk factors for lithium-induced nephrotoxicity include increasing age, duration of treatment, cumulative dose, lower initial eGFR, female gender, hypertension and diabetes, concomitant nephrotoxic drugs, nephrogenic diabetes insipidus and previous lithium toxicity.149 If lithium is used in renal impairment, toxicity is more likely and lithium toxicity increases the risk of renal impairment. Renal damage is more likely with chronic toxicity than acute. The manufacturer contraindicates lithium in severe renal impairment. Dosing: GFR 10–50mL/min avoid or reduce dose (50–75% of normal dose) and monitor levels; GFR <10mL/min avoid if possible, however if used it is essential to reduce dose (25–50% of normal dose). Lithium can be used successfully during haemodialysis.150 (Continued)

 Table 8.11 Anxiolytics and hypnotics in renal impairment. Drug Comments Buspirone25,27,34,36 <1% excreted unchanged; however, active metabolite is renally excreted. Dosing advice contradictory, suggests GFR 20–50mL/min start at a low dose and give twice daily; GFR <20mL/min avoid if possible due to accumulation of active metabolites; if essential, reduce dose by 25–50% if patient is anuric. Manufacturer contraindicates in severe renal impairment (GFR <20mL/min). Chlordiazepoxide25,27,36 1–2% excreted unchanged but chlordiazepoxide has a long-acting active metabolite that can accumulate. Dosing: GFR 10–50mL/min dose as normal renal function; GFR <10mL/min reduce dose by 50%. Monitor for excessive sedation. Manufacturer cautions in chronic renal disease. Long-term use may be associated with an increased risk of CKD.123 Clomethiazole25,27,34,160 (chlormethiazole) 0.1–5% of drug excreted unchanged in urine. Dose as in normal renal function but monitor for excessive sedation. Manufacturer recommends caution in renal disease. Clonazepam25,27,34,161 <0.5% of clonazepam excreted unchanged in urine. Dose adjustment not required in impaired renal function; however with long-term administration, active metabolites may accumulate so start at a low dose and increase according to response. Monitor for excessive sedation. Has been used for insomnia in patients on haemodialysis. Long-term use may be associated with an increased risk of CKD.123 Diazepam27,34,36,162 <0.5% is excreted unchanged. Dosing: GFR 20–50mL/min dose as in normal renal function; GFR <20mL/min use small doses and titrate to response. Long-acting, active metabolites accumulate in renal impairment; monitor patients for excessive sedation and encephalopathy. One case of interstitial nephritis with

diazepam has been reported in a patient with chronic renal failure. Long-term use may be associated with an increased risk of CKD.123 Eszopiclone163 <10% excreted unchanged in urine. No dose adjustment is needed in renal impairment. Gabapentin 100% excreted unchanged in urine, clearance is reduced in renal impairment resulting in higher plasma concentrations and longer elimination half-lives.164 As expected this may result in toxicity in renal impairment if doses are not reduced.165 Acute renal failure has been reported,166 as has myoclonus,167 altered mental status, fall and fracture when used in patients on haemodialysis for restless legs, itch and neuropathic pain.168,169 Has been used to treat pruritis, muscle cramps and restless legs syndrome in haemodialysis patients in RCTs.170–172 Dosing advice differs: GFR 15–60mL/min start low and increase according to response; GFR <15mL/min 300mg alternate days36,166 or 100mg at night then increase according to tolerability27,173 but check for toxicity as described above. Manufacturer has table of very specific dosing in renal impairment in SMPC.166 Drug Comments Valproate25,27,34,151–155 Approximately 2% excreted unchanged. Dose adjustment usually not required in renal impairment; however free valproate levels may be increased. Renal impairment, interstitial nephritis, Fanconi syndrome, renal tubular acidosis and renal failure have been reported. Risk factors for renal tubular dysfunction include being bedbound and low serum carnitine and phosphorus levels.156 Dose as in normal renal function, however in severe impairment (GFR <10mL/min) it may be necessary to alter doses according to free (unbound) valproate levels. Possibly less likely than lithum to cause chronic kidney disease in patients with bipolar disorder157,158 but data are conflicting.159 BPAD, bipolar affective disorder; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate. Table 8.10 (Continued)

Prescribing in hepatic and renal impairment CHAPTER 8 Drug Comments Lemborexant,45,174 suvorexant, daridorexant <1% excreted unchanged in urine. Manufacturers state no dose adjustment needed in renal impairment. Exposure to lemborexant may increase during severe renal impairment with a potential increased risk of somnolence.175 Lorazepam25,27,34,36,176–181 <1% excreted unchanged in urine, dose as in normal renal function but carefully according to response as some may need lower doses. Monitor for excessive sedation. Impaired elimination reported in two patients with severe renal impairment and also reports of propylene glycol in lorazepam injection causing renal impairment and acute tubular necrosis. However, lorazepam injection has been successfully used to treat catatonia in two patients with renal failure, and it is the drug of choice in status epilepticus for patients with renal disease.182 Melatonin <1% excreted unchanged in urine. Manufacturers state limited information on use in renal impairment, but numerous studies suggest melatonin may be renoprotective in acute kidney injury and chronic renal disease183,184 and beneficial for sleep in haemodialysis patients.185,186 Dose as for normal renal function but monitor for oversedation in severe impairment. Nitrazepam25,27 <5% excreted unchanged in urine. Dosing: GFR 10–50mL/min dose as in normal renal function; GFR <10mL/min start with small dose and increase slowly. Manufacturer advises reducing dose in renal impairment. Monitor patient for sedation and unsteadiness. Long-term use may be associated with an increased risk of CKD.123 Pregabalin Up to 99% excreted unchanged in urine. Acute renal failure reported.187 Associated with altered mental status and falls when used in patients on haemodialysis168 and myoclonus.188 Case report of seizure on abrupt cessation in patient with CKD.189 Used to treat uraemic pruritis and neuropathic pain in patients on haemodialysis190–192 and restless legs syndrome in CKD.193 Dosing advice differs; titrate dosing by tolerability and response for all GFRs; initial dose for GFR 30–60mL/min 75mg daily and max. 300mg daily; GFR 15–30mL/min 25–50mg daily and max. 150mg daily; GFR

<15mL/min 25mg daily and max. 75mg daily. Manufacturer has table of very specific dosing in renal impairment in SMPC.187 Oxazepam27,34,36,194 <1% excreted unchanged in urine. Dose adjustment may be needed in severe renal impairment. Oxazepam may take longer to reach steady state in patients with renal impairment. Dosing: GFR 10–50mL/min dose as in normal renal function; GFR <10mL/min start at a low dose and increase according to response. Monitor for excessive sedation. Promethazine25,27,34,36,195 Dose reduction usually not necessary; however, promethazine has a long half-life so monitor for excessive sedative effects in patients with renal impairment. Manufacturer advises caution in renal impairment. There is a case report of interstitial nephritis in a patient who was a poor metaboliser of promethazine. Temazepam25,27,34,36 <2% excreted unchanged in urine. In renal impairment the inactive metabolite can accumulate. Monitor for excessive sedative effects. Dosing: GFR 20–50mL/min dose as normal renal function; GFR <20mL/min dose as in normal renal function but start with 5mg. Zolpidem25,27,34,161,196 Clearance moderately reduced in renal impairment. No dose adjustment required in renal impairment. Zolpidem 1mg has been used to treat insomnia in patients on haemodialysis. One trial of use as a sleep aid in haemodialysis patients with pruritis.197 Associated with acute pyelonephritis in women.198 Long-term use may be associated with an increased risk of CKD.123 Zopiclone25,27,34,199,200 <5% excreted unchanged in urine. Manufacturer states no accumulation of zopiclone in renal impairment but suggests starting at 3.75mg. Dosing: GFR <10mL/ min start with lower dose. Interstitial nephritis reported rarely. Long-term use may be associated with an increased risk of CKD.123 CKD, chronic kidney disease; GFR, glomerular filtration rate; SMPC, summary of product characteristics. Table 8.11 (Continued)

778 The Maudsley® Prescribing Guidelines in Psychiatry CHAPTER 8 Table 8.12 Anti-dementia drugs in renal impairment. Drug Comments Donepezil25,27,201–203 17% excreted unchanged in urine. Dosing is as in normal renal function for GFR ≤10–50mL/min. Manufacturer states that clearance not affected by renal impairment. Single-dose studies find similar pharmacokinetics in moderate and severe renal impairment compared with healthy controls. Has been used at a dose of 3mg/day in an elderly patient with Alzheimer’s dementia on dialysis. Single case of rhabdomyolysis causing acute renal failure204 and one of donepezil-induced parkinsonism in end stage renal disease.205 Galantamine25,27 18–22% excreted unchanged in urine. Dose as in normal renal function for GFR 9–50mL/min and at GFR <9mL/min start at a low dose and increase slowly. Maximum 16mg/day in moderate impairment. Manufacturer contraindicates use in GFR <9mL/ min. Plasma levels may be increased in patients with moderate and severe renal impairment. Memantine25,34,206 Manufacturers recommend a 10mg immediate release dose if GFR 5–29mL/min; 10mg daily for 7 days then increased to 20mg daily if tolerated for GFR 30–49mL/min; no dose adjustment required for GFR >50mL/min. Extended release dose is 14mg daily for GFR 5–29mL/min. Renal tubular acidosis, severe urinary tract infections and alkalisation of urine (e.g. by drastic dietary changes, such as switching from carnivore to vegetarian diet) can increase plasma levels of memantine. Acute renal failure has been reported, and one case of encephalopathy in chronic kidney disease.207 Rivastigmine25,27 0% excreted unchanged in urine but manufacturer states caution is required for patients with renal disease because of an increased risk of adverse effects. Dosing advice for GFR <50mL/min start at a low dose and gradually increase. Steady-state plasma concentrations are not affected by renal function.208 GFR, glomerular filtration rate. Table 8.13 Other psychotropic drugs in renal impairment. Drug Comments Bremelanotide45,209 64.8% excreted unchanged in urine. Manufacturer states GFR 30–89mL/min no dosage adjustment necessary; caution for GFR <30mL/min as increased adverse

effects (nausea and vomiting). Exposure is increased in renal impairment. Case report of Melotan II (bremelanotide is a variation of Melotan II) and rhabdomyolysis and renal dysfunction.210 Deutetrabenazine211 No clinical studies in renal impairment. Data limited, no specific dosing advice. Pitolisant45,212 <2% excreted unchanged in urine. Dosing: GFR 15–59mL/min 8.9mg daily, increase after 7 days to max. 17.8mg once daily;213 GFR <15mL/min not recommended.213 Peak concentrations and exposure increased in all stages of renal impairment. Solriamfetol45,214 95% excreted unchanged in urine. Dosing: GFR 60–89mL/min no dose adjustment is required; GFR 30–59mL/min 37.5mg once daily, increased to max. of 75mg once daily after 5 days; GFR 15–29mL/min 37.5mg once daily; GFR <15mL/min not recommended. In moderate or severe renal impairment risk of increased blood pressure and heart rate because of the prolonged half-life. Increased exposure and t1/2 in all stages of renal impairment particularly end stage renal disease.215 Valbenazine45 <2% excreted unchanged in urine. No adjustment is necessary. Urinary retention reported as adverse effect in clinical trials. GFR, glomerular filtration rate.

16 - Summary of recommended psychotropics in renal

Summary of recommended psychotropics in renal impairment

Prescribing in hepatic and renal impairment CHAPTER 8 Summary of recommended psychotropics in renal impairment Where renal function declines while on existing drug treatment, rule out existing drugs as a cause of reduced function and continue at a dose suggested in Tables 8.9–8.14. Where new drug treatment is required follow the suggestions in Table 8.15. Table 8.14 Attention deficit hyperactivity disorder (ADHD) drugs in renal impairment. Drug Comments Atomoxetine24,216 No dose adjustment required. Atomoxetine may exacerbate hypertension in patients with end stage renal disease. Dexamfetamine24,217 30–40% excreted unchanged in normal urine pH (renal elimination is decreased under alkaline conditions, increased under acidic conditions). Limited data in renal disease, manufacturers state that peak plasma levels could be higher and elimination prolonged. For the transdermal patch: GFR 15–30mL/min max. dose 13.5mg/ 9 hours; GFR <15mL/min max. dose 9mg/9 hours. For oral dosing: start at low doses and increase cautiously. Lisdexamfetamine24,218 Reduced clearance in patients with severe renal insufficiency. GFR 15–30mL/min max. dose 50mg/day; GFR <15mL/min max. dose 30mg/day.219 Methylphenidate24,220 <1% excreted unchanged in urine. Limited data in renal disease, but pharmacokinetics suggest dose adjustment is unlikely to be necessary. Two case reports (one in a patient undergoing peritoneal dialysis) suggest no change in clearance of methylphenidate in end stage renal disease.221 One case report of use in polycystic kidney disease.222 GFR, glomerular filtration rate. Table 8.15 Recommended psychotropics in renal impairment. Drug group Recommended drugs Antipsychotics No agent clearly preferred to another, however: ■ ■Avoid sulpiride and amisulpride ■ ■Avoid highly anticholinergic agents because they can contribute to urinary retention ■ ■First-generation antipsychotic – suggest haloperidol 2–6mg a day ■ ■Second-generation antipsychotic – suggest olanzapine 5mg a day Antidepressants223 No agent

clearly preferred to another, however reasonable choices are: ■ ■Sertraline but poor efficacy data in renal disease ■ ■Citalopram (NB QTc-prolonging effects and greater risk of sudden death in those on haemodialysis vs other selective serotonin reuptake inhibitors) ■ ■Fluoxetine but consider long half-life and need for alternate day dosing at lower GFRs Mood stabilisers No agent clearly preferred to another, however: ■ ■Avoid lithium if possible ■ ■Suggest start one of the following at a low dose and increase slowly, monitor for adverse effects: valproate or lamotrigine Anxiolytics and hypnotics No agent clearly preferred to another, however: ■ ■Excessive sedation is more likely to occur in patients with renal impairment, so monitor all patients carefully ■ ■Lorazepam and zopiclone are suggested as reasonable choices Anti-dementia drugs No agent clearly preferred to another, however: ■ ■Rivastigmine is a reasonable choice GFR, glomerular filtration rate.

17 - References

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