03 - Antipsychotics in hepatic impairment2

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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)

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.

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