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.

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