Antiseizure Medications and Liver Health:

A Summary of Drug-Induced Liver Injury (DILI)

INTRODUCTION

The table below summarizes current knowledge on the potential hepatotoxicity of antiseizure medications (ASMs) available for prescription in the United States. The table is updated to March 2025. It is aimed at assisting clinicians who provide care for persons with epilepsy recognize the risk, manifestations, and management of ASM-induced toxicity.

BACKGROUND

Whereas the effects of older ASMs on the liver have been extensively studied, data on some of the newer ASMs are more sporadic. The table summarizes current data and provides a summary of labelling information. In addition, it includes data on drug interactions that may increase the risk of liver injury and on emerging biomarkers of ASM-induced hepatotoxicity.

TARGET AUDIENCE

Whereas the effects of older ASMs on the liver have been extensively studied, data on some of the newer ASMs are more sporadic. The table summarizes current data and provides a summary of labelling information. In addition, it includes data on drug interactions that may increase the risk of liver injury and on emerging biomarkers of ASM-induced hepatotoxicity.

SOURCES

- The table is followed by a reference list.
- LiverTox[1] is a resource produced by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). It provides information on liver injury attributable to medications and selected herbal and dietary supplements. Monographs are updated periodically. The LiverTox's likelihood score is more accurate for drugs that have been extensively used for a prolonged period and is less accurate for more recently approved medications and medications that have not been used widely. This may lead to discrepancies between the likelihood score E* (unproven but suspected rare cause of clinically apparent liver injury, particularly with high doses) and a recommendation for routine monitoring of hepatic function (e.g., for cannabidiol and ethosuximide).1 See table legend for the score categories.

PRECAUTIONS FOR ASMS

- The FDA labels of some hepatotoxic drugs such as levoketoconazole and pexidartinib warn against their combinations with other hepatotoxic agents. Note that some herbal supplements (e.g., ashwagandha, turmeric, kratom, green tea extract, and Garcinia cambogia) are hepatotoxic as well.
- General recommendations for the management of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) are summarized as a comment.

IMPORTANT NOTES

- This document summarizes prescribing and literature data and is not intended to constitute treatment recommendations.
- Product information is updated on an ongoing basis. The FDA database product information sources for each ASM, available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm, should be consulted for the most current information.

Main characteristics of hepatic injury	Timing	Incidence/prevalence	Predictive Factors	Actionable Reccomendations	Outcomes & management	Emerging biomarkers
Adrenocorticotropic Hormone (ACTH): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : A**		
No data on ACTH specifically. Corticosteroids can cause hepatic enlargement, steatosis, glycogenosis, and worsen nonalcoholic steatohepatitis. Long-term use may exacerbate chronic viral hepatitis. Withdrawal or pulse therapy can reactivate hepatitis B or trigger autoimmune hepatitis, both potentially fatal. High-dose IV corticosteroids, mainly methylprednisolone, have been linked to acute liver injury which can result in liver failure and death.[1]	Long-term use or on withdrawal [1]	Sedation and dizziness often reported; may also cause confusion.	N/A	None in FDA monograph	N/A	N/A
Brivaracetam (BRV): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : E**		
Theoretically may be a hypersensitivity reaction if it occurs;[1] Severe cutaneous adverse reactions including SJS reported.[3] However, BRV would likely be a safe medication for individuals with liver disease[4]	N/A	Rare. In a pharmacovigilance study, no increase in odds ratio of hepatotoxicity[2]	N/A	Minor serum transaminase elevations rarely require dose changes, but levels above 5× ULN warrant modification and evaluation for other causes.[1]	N/A	N/A
Cannabidiol (CBD; data related only to the FDA-approved oral preparation): Routine hepatic function monitoring[2] is recommended.				**LiverTox likelihood score (A, high; E, low)[1] : E***		
Transaminase elevations during clinical trials. In post marketing setting, cases of cholestatic or mixed patterns of liver injury (i.e., based on calculated ratio of [ALT/ULN]/[ALP/ULN] <2 and 2-5, respectively); elevations in ammonia levels seen in post marketing in some patients who	1 to 8 weeks after starting therapy[1,2,8] though could be seen as late as 18	Dose-related elevations of liver transaminases (ALT or AST): ALT 3 X ULN occurring in 13% (10-20 mg/kg/day) and 12% (25 mg/kg/day) in CBD treated patients vs 1% in placebo.[2] Less than 1% treated with	Concomitant use of VPA or CLB, CBD daily doses ≥ 1000 mg or 20 mg/kg per day;[2,8,9] in 16 healthy volunteers, no correlation between baseline patient characteristics, CYP2C19 genotype, or CBD plasma concentrations and	Obtain baseline ALT and AST and total bilirubin; recommendations for dose adjustment and slower titration in patients with preexisting moderate or severe hepatic impairment as described by Child-Pugh B or C are available in the package label.[2] Serum transaminases and total bilirubin levels should be obtained at 1 month, 3 months, and 6 months after	In ~2/3 cases, resolution of transaminase elevations occurs with dose-reduction or discontinuation of CBD or VPA.	N/A

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also had elevated transaminases;1 symptoms may be consistent with hepatitis or hypersensitivity;5 cases of modest bilirubin elevations.6 No reported cases of severe DILI.6 Hepatotoxicity mainly driven by the parent drug.7	months after treatment initiation per clinical trials[1]	CBD has ALT or AST levels > 20 X ULN. ALT elevations > 3 X ULN in 30% of patients taking both concomitant VPA and CBZ.[2] In healthy adult volunteers, ALT > ULN in 44% of 16 individuals treated with 1,500 mg/day CBD, ALT > 5 X ULN in 31%;5 in a meta-analysis of 12 clinical trials with 1,229 participants, odds ratio for CBD-induced liver enzyme elevation 5.85 and for CBD-induced DILI 4.829	transaminase elevations.[5] Concurrent elevations in ammonia levels may be seen with concomitant use of VPA, CLB or both[2]	initiation of treatment with CBD, and periodically thereafter or as clinically indicated, and within 1 month of changes in dosage and addition of or changes in treatment known to impact the liver.[2] Consider more frequent monitoring of serum transaminase and total bilirubin if concomitant treatment with VPA or if elevated at baseline. If the patient develops clinical signs/symptoms suggestive of hepatotoxicity, then immediately check serum transaminases and total bilirubin and either interrupt or discontinue treatment as appropriate.[2] Consider dose adjustments or discontinuation of VPA or CLB if liver enzyme elevations and if ammonia elevations occur. More specifically, discontinue treatment if serum transaminases 2 X ULN and total bilirubin 2 X ULN. Discontinue treatment in patients with prolonged, sustained serum transaminase elevations of 5 X ULN[2]	In 1/3 cases, elevations spontaneously resolved during continued therapy without dose reduction[5,6]	N/A
Carbamazepine (CBZ): Routine hepatic function monitoring[2] is recommended.				**LiverTox likelihood score (A, high; E, low)[1]** : A		
DILI most often in the setting of DRESS,[10] most commonly with an enzyme elevations pattern of a mixed or cholestatic injury; in fatal cases bridging, submissive, or massive necrosis; might also be associated with the vanishing bile duct syndrome[1,11]	1 to 8 weeks after starting therapy[1]	Several hundred cases of clinically apparent hepatotoxicity; high risk for DILI vs. all non-ASMs[12] In veterans, 2.6 hospitalizations for severe DILI per 10,000 person-years (95% CI, 1.2-5.5)[13] The most frequent drug causing DILI-DRESS (13% of cases) in some registries;[10] high relative odds ratio for SJS[14] Transient serum aminotransferase elevations: 1%-22%;	Common cross-reactivity with other aromatic ASMs (PHT, PB, PRM, OXC, LTG);[1] higher risk in children undergoing polytherapy;[4] association with HLA-B*15:02 or HLA-A*31:01 less demonstrated than in cutaneous reactions.[1] However, 4 of 12 CBZ-DILI European patients were HLA-A*31:01 carriers and DILI odds ratio was 7 [15]	Conduct baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease; CBZ should be discontinued, based on clinical judgment, upon newly occurring or worsening clinical or laboratory evidence of liver dysfunction/hepatic damage/active liver disease.[2] In the case of severe CBZ hypersensitivity, avoid exposure to other aromatic ASMs (PHT, PB, PRM, OXC, LTG).[1] Combinations of strong enzyme inducers and lorlatinib are contraindicated. CBZ should be switched to a non-inducer ASM 3 half-lives (~3 days on chronic treatment) before the onset of lorlatinib treatment[2] #	Hepatotoxicity is usually rapidly reversible with stopping therapy; severe injury may progress to acute liver failure and death, particularly in patients presenting with a hepatocellular pattern of serum enzyme elevations;[1]	HLA-B*15:11[16] and B*57:01[15] suggested as SJS/TEN risk alleles

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		GGT elevations, most patients treated with CBZ; > 5-fold GGT elevation less frequent[1]			once hepatotoxicity has developed, mortality rate is about 25%.[4] The effectiveness of corticosteroids for the hepatic components of the hypersensitivity syndrome is uncertain[1 #]	
Hepatotoxicity without immunoallergic features; hepatocellular; more likely to be more severe than in DRESS[1]	6 to 12 months after starting[1]					
CBZ may enhance the hepatotoxicity of acetaminophen (when acetaminophen is given at high and frequent doses[17-19] and that of isoniazide[2,20,21] due to enhanced formation of toxic metabolites. CBZ may cause severe hepatoxicity when combined with lorlatinib[2]						
Cenobamate (CNB): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : D**		
Low-to-moderate rate of serum aminotransferase elevations during therapy (clinical trial data)[1]		1-4% transaminase elevation	The cross-reactivity of CNB hypersensitivity with aromatic ASMs (PHT, CBZ, LTG) is unknown, but its structure suggests possible sensitivity. FBM, a structurally related carbamate, is a known DILI cause.[1]	Slow up-titration as described in package label for reducing DRESS risk;[2] generally, patients who have developed serious hypersensitivity reactions to CNB should discontinue therapy promptly and avoid reexposure[1 #]	N/A	N/A

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Clinically apparent liver injury usually in the context of a multiorgan hypersensitivity syndrome such as DRESS.[1]	3-6 weeks after starting therapy[1]	3 of 953 patients developed DRESS in rapid (4-6 week) titration with elevated transaminases; none out of > 1339 open-label exposures with slow, 12 weeks titration[1]			once hepatotoxicity has developed, mortality rate is about 25%.[4] The effectiveness of corticosteroids for the hepatic components of the hypersensitivity syndrome is uncertain[1 #]	
A case of hepatic enzyme elevation with steatosis and hepatomegaly after twenty years of VPA administration and in concomitance with the introduction of CNB (rate of CNB up-titration not reported)[22]						
Clobazam (CLB): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : E**		
CLB-associated DRESS and SJS.[2,23,24] See also CBD for CLB-CBD combinations	Hypersensitivity reactions typically occur 2 weeks to 8 weeks after starting the drug[24]	10 DRESS cases involving children and adults reported to FAERS by 2023.[24] Reporting odds ratio for DILI vs. all non-ASM reports, 1.67, but it may be difficult to separate CLB hepatotoxic effects from other medications[12]	N/A	N/A	N/A #	N/A
Clonazepam (CZP): Routine hepatic function monitoring[2] is recommended.				**LiverTox likelihood score (A, high; E, low)[1] : D**		
Benzodiazepines are rarely	Few weeks	Exceedingly rare.[1] In	No data on	Periodic liver function tests are advisable	Reported cases	N/A

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associated with DILI and have been associated with cholestatic or mixed, less likely hepatocellular pattern, typically mild to moderate severity and self-limited. Isolated instances of hepatotoxicity have been reported for clorazepate and clonazepam[1] (also see CLB)	to few months[1]	pharmacovigilance studies, no increase odds ratio of hepatotoxicity[2,12]	benzodiazepine cross-reactivity; assume some degree of cross-sensitivity.[1]	during long-term therapy with CZP[2]	followed by complete recovery[1]	N/A
Eslicarbazepine Acetate (ESL): Routine hepatic function monitoring[2] is not recommended but baseline evaluation is recommended.				**LiverTox likelihood score (A, high; E, low)[1] : D**		
Transient elevations in ALT above 3 X ULN in less than 1%. [1]	Days to months.[1] DRESS: in one case, 12 days from ESL treatment onset.[25] Typically 2-8 weeks[2]	Rare - less than 1%.[1] In one pharmacovigilance study, no increase in odds ratio of hepatotoxicity.[12] In another, 17 reported cases of hepatobiliary disorders, 3 SCAR cases. Odds ratio for DRESS in the pediatric group, 9.93[26]	No data on cross-sensitivity to hepatotoxicity between ESL and other ASMs, but its structure suggests potential cross-sensitivity with OXC and partial cross-sensitivity with aromatic ASMs like PHT, CBZ, and LTG.[1] Elevated transaminases with high bilirubin (without obstruction) is an important predictor of severe liver injury.[2]	Baseline evaluations of liver lab tests are recommended;[2] Discontinue in patients with jaundice or evidence of severe liver injury.[2] Patients with a prior DRESS reaction with OXC or ESL should not be treated with ESL.[2] # Individuals of Han Chinese or Thai origin should be screened for HLA-B*15:02 before starting treatment with drugs chemically related to CBZ. If patients of these origins are tested positive for HLA-B*15:02, the use of ESL may be considered if the benefits exceed risks. Testing other genetically at-risk populations for the presence of HLA-B*15:02 may be considered. If patients of European or Japanese origin are known to be positive for HLA-A*31:01 allele, the use of CBZ-related compounds may be considered if the benefits exceed risk[3]	Rapid recovery[1] #	N/A
Reports of DILI, most hepatocellular pattern, one case with jaundice[1,26]						
DRESS and SJS have been reported [2,25]						

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Ethosuximide (ESM): Routine hepatic function monitoring[2] is recommended.				**LiverTox likelihood score (A, high; E, low)[1] : E***		
Can increase GGT levels without an increase in serum aminotransferase levels, rare transient elevations in serum aminotransferase levels. Mild and asymptomatic liver injury with a mixed-cholestatic-hepatocellular pattern can be seen in the setting of hypersensitivity syndrome.[1]	Hypersensitivity typically 2-8 weeks[1]	Exceedingly rare (only a few case reports).[1] In a pharmacovigilance study, no increase odds ratio of hepatotoxicity[12]	No clear cross-reactivity with other ASMs[1]	Periodic liver function monitoring advised.[2] Should be administered with extreme caution to patients with known liver (or renal) disease.[2] Liver injury typically recurs rapidly with re-exposure, which should be avoided[1 #]	Rapid recovery[1 #]	N/A
Reported DRESS cases[27,28]						
Everolimus (EVL): Routine hepatic function monitoring[2] is not recommended except in the patient information section of the PI.				**LiverTox likelihood score (A, high; E, low)[1] : E***		
Asymptomatic serum enzyme elevations are common. Rarely require dose modification. EVL is immunosuppressive, can reactivate chronic hepatitis[1]	N/A	Serum enzyme elevations up to 25%, only 1-2% greater than 5 X ULN. Rarely require dose modification[1]	Chronic viral hepatitis[1]	Routine screening for HBsAg and anti-HBc before starting therapy (particularly those undergoing organ transplantation).[1] If HBV or HCV positive, offer prophylaxis or monitoring for de novo appearance or rise in levels of HBV DNA. Reactivation should be treated with an oral analog with potent activity against hepatitis B (entecavir or tenofovir alafenamide) nucleoside[1]	Typically minimal sequelae but reactivation of Hepatitis B can be severe and fatal[1]	N/A
Felbamate (FBM): Routine hepatic function monitoring[2] is recommended				**LiverTox likelihood score (A, high; E, low)[1] : B**		
Hepatocellular liver injury;[1] although some reports described dark urine and non-specific prodromal symptoms (e.g., anorexia, malaise, and gastrointestinal symptoms), in others it was not clear if any prodromal symptoms precede the onset of jaundice[2]	1-6 months after starting therapy.[1] Earliest onset 3 weeks after initiation.	3.5% transaminase elevation in controlled clinical trials.[2] Clinically apparent hepatotoxicity in 1 in 18,500 - 25,000 exposures, often with severe outcome.[29] Rate of 6 cases of liver failure leading to death	It is not known whether hepatic failure risk changes with the duration of exposure, or whether the FBM dose or concomitant use of other ASMs affect the incidence of hepatic failure.[2] Females might be at a higher risk than males,[29] although a	Boxed Warning: physicians should obtain written informed consent prior to initiation. Discontinue if either AST or ALT increases >= 2 x ULN or clinical signs/symptoms of liver failure and do not resume.[2] Initiate only in those without liver disease and normal baseline serum transaminases. Frequent periodic monitoring of hepatic function recommended before, during, and after	More than a dozen instances of liver failure and death;[1] of the cases reported, about 67% resulted in death or liver transplantation, usually within 5	N/A

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	Death / liver transplantation within 5 weeks of onset of signs / symptoms of liver failure[2]	or transplant per 75,000 patient years of use (underestimate)[2]	pharmacovigilance study involving patients <18 years old did not confirm this observation[30]	the completion of FBM therapy, along with comprehensive metabolic panel and blood counts. Suggested frequency during treatment: every two weeks or less for the first 3 months, then every 6 to 12 months thereafter.[31] It has not been proved that periodic serum transaminase testing will prevent serious injury but it is generally believed that early DILI detection and immediate withdrawal of the suspect drug enhances the likelihood for recovery. Patients who develop signs of hepatocellular injury while on FBM and are withdrawn from the drug for any reason should not be considered for re-treatment.[2]	weeks of the onset of signs and symptoms of liver failure[2]	
Fenfluramine (FFA): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : Not in LiverTox**		
Label does not mention serum transaminase elevation in clinical trial or concern for hepatotoxicity;[2] a case of vanishing bile duct syndrome reported in a conference abstract[32]	N/A	Unknown	N/A	N/A	N/A	N/A
Gabapentin (GBP): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : C**		
Because GBP is not hepatically metabolized no studies in hepatic disease were performed per the label. However, there are rare individual case reports of hepatocellular, cholestatic, and mixed injury, though causal relationship with GBP not always clear.[1] Rare cases of DRESS.[2] In general, GBP is well tolerated in patients with hypersensitivity reactions to other ASMs[1]	Time to liver injury, 1-8 weeks[1]	Large pharmacovigilance studies were unable to establish an increased risk of hepatotoxicity associated with GBP;[12,33] lower risk than older ASMs[34] In veterans, 0.8 hospitalizations for severe DILI per 10,000 person-years (95% CI, 0.6-1.0)[13]	There is no information about cross-reactivity with other compounds having similar structures (e.g., PGB)	N/A [#]	Cases of hepatic injury from GBP resolved fully with no chronic injury. No reports of GBP causing acute liver failure or chronic injury.1 [#]	N/A

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Ganaxolone (GNX): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : Not in LiverTox**		
Label does not mention GNX causing hepatotoxicity[2]. Patients with abnormal liver function were excluded from clinical trial for CDKL5 deficiency disorder[35]	N/A	N/A	N/A	N/A	N/A	N/A
Lacosamide (LCM): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : D**		
Hepatocellular pattern of injury. ALT elevations in prelicensure trials.[1] Rare isolated reports of clinically apparent liver injury but confounded by multiple other ASMs or hepatic ischemia[1]	Within a few days to several months from initiation[1]	In prelicensure trials, LCM plus standard ASMs caused ALT >3× ULN in 0.7% (7/935) of patients vs. 0/356 on placebo.[1] Pharmacovigilance studies[12,36] found no increased liver toxicity risk.	N/A	N/A+F31:I39	N/A	N/A
Lamotrigine (LTG): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : A**		
Hypersensitivity or an immunological response to a metabolically generated drug-protein complex.[1] Liver injury includes rare elevated serum aminotransferase levels during long-term LTG and hepatocellular injury occurring as part of anticonvulsant hypersensitivity syndromes such as SJS/TEN or DRESS (most of LTG-DILI cases;[10,11] In these latter cases, liver biopsy shows portal inflammation, hepatocellular necrosis and bile duct proliferation. LTG has also been linked to rare instances of HL,	Ranging from one to several weeks from the initiation of LTG; nearly all cases of life-threatening hypersensitivity syndromes caused by LTG have	>1% develop elevations in serum aminotransferase levels during long-term LTG therapy	Higher incidence of life-threatening rashes in pediatric patients than in adults.[2] High starting doses, rapid rate of titration, and concomitant VPA administration are associated with increased risk of DRESS where hepatotoxicity may be seen[2] - 60% of DILI cases occurred after a rapid dose increase[34]	Boxed warning for SJS. Up-titration regimens listed in package labelling, with a special regimen for LTG-VPA. LTG should be discontinued at the first sign of rash, unless the rash is clearly not drug related. It is recommended that LTG not be restarted in patients who discontinued due to rash associated with prior treatment with LTG unless the potential benefits clearly outweigh the risks.[2] Consider avoiding PHT, PB, CBZ in persons with hepatotoxicity of LTG as there may be some degree of overlap in hypersensitivity response.[1] No genetic test is currently recommended in FDA labelling [#]	LTG hepatotoxicity is usually reversible within days of stopping the drug. Multiorgan failure cases may involve DIC, rhabdomyolysis, and renal failure. Prompt discontinuation enables recovery within 1–2 weeks, while delayed	Strong association of LTG-DILI with A*32:01 in African-Americans[43] HLA-A*24:02 linked to LTG SCAR in Asian populations[44] and to LTG-DRESS in European populations[45,46] but the associations are weak. Also,

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which include liver injury, hepatitis, and liver failure.[1]	occurred within 2 to 8 weeks of treatment initiation. Isolated cases have occurred after prolonged treatment (e.g., 6 months)[2]				withdrawal can cause irreversible liver failure. A reported LTG-DRESS case required liver transplant.[42] LTG-HL can be life-threatening and is typically treated with immunosuppression, including corticosteroids, etoposide, and sometimes emapalumab.[1,#]	a higher risk of LTG-SJS in Chinese HLA-B*15:02 carriers but the association is weaker than with CBZ.[16,47]
Reported cases of cholestatic hepatitis with features suggestive of vanishing bile duct syndrome[34] and of chronic liver injury[37]		Clinically apparent hepatotoxicity: 1:2,000 to 1:10,000 treated patients.[1] Pharmacovigilance studies an association of LTG with an increased hepatotoxicity risk.[12,14,30,33,36] In veterans, 1.0 hospitalizations for severe DILI per 10,000 person-years (95% CI, 0.4-2.5)[13] The most common ASM to cause DILI in the FAERS reporting system,[34] and the LTG/VPA combination the second most frequently reported ASM combination associated with DILI in children.[30] Among the top drugs associated with reports of DRESS38 and SJS/TEN[39-41]				

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Levetiracetam (LEV): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : C**		
Rare elevations of serum aminotransferases and ALP[1] but also cases of clinically apparent DILI, both hepatocellular and cholestatic liver injury;[12,33] A reported case of vanishing bile duct syndrome under treatment with temozolomide and LEV[48]	Ranging from one week to 5 months from initiation of LEV[1]	In recent pharmacovigilance studies, LEV-DILI was 1.56 times higher than that of all non-ASMs.[12] Other studies supported an increased odds ratio for LEV-DILI in pediatric[30] and geriatric[33] patients. In pediatric patients, LEV was the second most commonly reported ASM in association with DILI.[30] In veterans, 1.3 hospitalizations for severe DILI per 10,000 person-years (95% CI, 0.6-3.2)[13]	No evidence of cross-sensitivity to hepatic injury between LEV and other ASMs[1]	N/A [#]	Many reports noted asymptomatic liver enzyme elevations and cases of acute liver failure from LEV, including one requiring transplantation.[1,2] In FAERS reports, most patients were hospitalized, received treatment, and two died. In most cases where discontinuation details were available, DRESS symptoms improved after stopping the drug.[24] Chronic injury from LEV therapy has not been reported.[1]	N/A
DRESS cases[1,2,24]	DRESS, typically 2-8 weeks from initiation[24]	32 cases of DRESS in LEV-treated children and adults reported to FAERS by 2023[24]				

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Oxcarbazepine (OXC): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : C**		
Hepatocellular toxicity with chronic use. Rare instances of clinically apparent drug induced liver disease or occurring in setting of DRESS or SJS[1,49]	If occurring in setting of hypersensitivity syndrome, 2 to 8 weeks after starting therapy[1]	Rarely causes hepatocellular toxicity and may be related to structural similarity to CBZ. The third-highest DILI risk among ASMs in one pharmacovigilance study.[12] In pediatric patients, the fourth most reported ASM in association with DILI and the second most commonly implicated ASM in hypersensitivity cases. Increased odds ratio for transaminase and GGT elevations[30,33]	~25–30% of patients with CBZ hypersensitivity also react to OXC.[2] Liver function monitoring is especially useful in pediatric patients.[30] Higher SJS risk in HLA-B*15:02 alelle carriers, particularly in those with South-East Asian origin, though weaker than with CBZ.	Patients should be asked about prior CBZ hypersensitivity; OXC should be used only if benefits outweigh risks. Discontinue OXC immediately if hypersensitivity occurs. [2, 50] Consider avoiding aromatic ASMs (PHT, PB, CBZ) in cases of severe OXC hypersensitivity. [1,2,50] Test for HLA-B15:02 allele in genetically at-risk populations before starting OXC and avoid use if positive unless benefits outweigh risks. Consider avoiding other SJS/TEN-associated drugs in HLA-B15:02 positive patients when alternatives are available. [2, #]	OXC hepatotoxicity is usually rapidly reversible with stopping therapy and improvements begin within days. In cases of severe injury, progression to acute liver failure and death can occur. Corticosteroids have been used but with uncertain effectiveness.[1 #]	N/A
Perampanel (PER): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : E**		
Rare DRESS cases where liver injury may occur.[1] Abnormal hepatic tests have been reported, but might be associated with concomitant treatments[51]	N/A	In phase 3, adverse events related to hepatobiliary parameters occurred in 0.4% of PER patients and 0% of placebo patients. No event was serious or led to PER discontinuation.[52] Low odds of DILI with PER[12]	No suspected cross-sensitivity to hepatotoxicity between PER and structurally dissimilar ASMs like PHT or CBZ.[1]	If hepatic enzymes elevation is observed, monitoring of liver function should be considered.[3 #]	N/A. [#]	N/A

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Phenobarbital (PB): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : B**		
Aminotransferase elevations[1]	During long-term therapy[1]	1%[1]		PB is contraindicated in patients with hypersensitivity to PB or other barbiturates. Consider alternatives if there's a history of hypersensitivity to structurally similar drugs like carboxamides (e.g., CBZ) and hydantoins (e.g., PHT) in the patient or immediate family. If hypersensitivity signs appear, evaluate immediately and discontinue PB if no alternative cause is found. Strong enzyme inducers and lorlatinib are contraindicated; switch PB to a non-inducer ASM 3 half-lives (~10 days) before lorlatinib treatment.[2]	Improvements usually begin within 5 to 7 days of stopping the drug, completed within 1 to 2 months. Severe injury can lead to acute liver failure and death. Corticosteroid effectiveness is uncertain. Prolonged cholestasis can occur.[1 #]	N/A
Clinically apparent hepatotoxicity: abrupt onset, ranges from mild to severe, may be fatal; typically, in the setting of anticonvulsant hypersensitivity syndrome (SJS or DRESS); serum enzyme elevation pattern can be hepatocellular or cholestatic; in biopsy, mixed hepatitis-cholestatic injury, prominence of eosinophils, and occasionally granulomata. Putative mechanism: hypersensitivity or an immunological response to a drug-protein complex[1] May cause severe hepatotoxicity when combined with lorlatinib[2]	1 week to months after therapy onset[1]	Rare.[1] However, reported odds ratio for DILI vs. all non-ASM reports, 2.91[12]	Cross-reactivity with other aromatic ASMs (PHT, CBZ, PRM, and LTG)[1]			

Main characteristics of hepatic injury	Timing	Incidence/prevalence	Predictive Factors	Actionable Reccomendations	Outcomes & management	Emerging biomarkers
Phenytoin (PHT) and Fosphenytoin (FOS): Routine hepatic function monitoring2 is not recommended.				**LiverTox likelihood score (A, high; E, low)[1]** : A		
Transient serum aminotransferase (< 3 X normal) and prolonged GGT elevations without apparent liver injury[1]		Common[1]	Hepatotoxicity more common in African Americans,[4,34] those with personal or family history of hypersensitivity reactions, and in immune-suppressed patients. Cross-sensitivity with other aromatic ASMs (PB, CBZ, LTG and ETX) can occur but not invariable[1]	PHT is contraindicated in patients with prior acute hepatotoxicity or hypersensitivity to PHT, its inactive ingredients, or other hydantoins. Consider alternatives to structurally similar drugs like carboxamides (e.g., CBZ), barbiturates, succinimides (e.g., ETX), and oxazolidinediones (e.g., trimethadione). If the patient or immediate family has a history of hypersensitivity to these drugs, avoid PHT.[2] Consider avoiding PHT as an alternative to CBZ in patients who are positive for HLA-B*15:02 or in CYP2C9*3 carriers.[53] In patients with a CYP2C9 variant, measure plasma PHT levels 7–10 days after starting or adjusting doses instead of 4–5 days. In the Netherlands, CYP2C9 genotyping before PHT maintenance therapy was suggested to be essential for drug safety.[16] Rechallenge is not recommended.[1] Combinations of strong enzyme inducers and lorlatinib are contraindicated. PHT should be switched to a non-inducer ASM 3 half -lives (~5 days) before the onset of lorlatinib treatment[2 #]	Use of PHT may be continued[1]	HLA-B * 53:01 in African Americans (both DILI and DRESS, odds ratio 9.2); was carried by 8 of 9 PHT DILI cases involving African Americans[43] HLA-B*15:02 increases SCAR risk[54] but association is weaker than with CBZ.[16,47] Southeast Asian carriers of decreased function CYP2C9*3 have increased SCAR risk, odds ratio 11 (+ decreased PHT clearance)[2,55,5]
Most commonly hepatocellular or mixed pattern (rarely cholestatic);[1] hypersensitivity features (e.g., DRESS) in 70% of hepatic injury cases[1,4,34,57] Cases of prolonged jaundice resembling vanishing bile duct syndrome[1] PHT can enhance the hepatotoxicity of acetaminophen - acetaminophen plasma concentrations should not be used to guide treatment[58-60] May	2-8 weeks after initiation of therapy[1]	Hepatotoxicity 1 per 10,000 to 1 per 50,000 exposures;[4] 4th most common drug associated with DILI among liver transplant recipients in the US between (1990-2002).[61] Reporting odds ratio for DILI vs. all non-ASM reports, 2.40.[12] In veterans, 2.1			Most resolve within 1 to 2 months of stopping PHT but can be fatal.[1] Mortality rate after severe liver involvement is 13%.[4] Acute PHT hepatitis with jaundice has a	

Main characteristics of hepatic injury	Timing	Incidence/prevalence	Predictive Factors	Actionable Reccomendations	Outcomes & management	Emerging biomarkers
cause severe hepatotoxicity when combined with lorlatinib[2]		hospitalizations for severe DILI per 10,000 person-years (95% CI, 0.8-5.7)[13] High relative odds ratio for SJS.14 Eight serious cutaneous reactions in 8,888 new PHT users[62]			jaundice has a greater than 10% fatality rate.[1 #]	
Pregabalin (PGB): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : C**		
Most hepatic injury cases were mild, frequently without jaundice. Both cholestatic and hepatocellular patterns of injury have been reported. Some severe cases with marked jaundice and prolongation of the prothrombin time.[1] In a pharmacovigilance study, 2 of 5 deaths in PGB-treated patients were hepatic-related (acute hepatitis)[63]	Symptoms of liver injury arising within 3 to 14 days[1]	Rare.[1] The most common suspect ASM in DILI cases in the elderly,[33] but no increased odds ratio or disproportional PGB hepatotoxicity.[12,33] In veterans, 1.1 hospitalizations for severe DILI per 10,000 person-years (95% CI, 0.6-2.1)[13]	In a pharmacovigilance DILI study in the elderly, the most frequent drug combination was PGB/acetaminophen[33]	N/A	All cases resolved after the medication stopped without evidence of residual injury[1]	N/A
Primidone (PRM): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : E***		
Can lead to increases in GGT levels. Elevated ALP levels were largely related to bone metabolism. Associations of PRM with hepatotoxicity are not strong, but it can interfere with porphyrin metabolism and cause worsening of porphyria[1]	N/A	In pharmacovigilance studies, no increase odds ratio of hepatotoxicity[12]	Potential cross-reactivity with PHT and PB in causing anticonvulsant hypersensitivity syndrome[1]	N/A	N/A	N/A
Rufinamide (RUF): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : E***		
Rare ALT elevations above 3 X ULN; two cases of children who	Within one month of	In a pharmacovigilance study, no reports of	Children younger than 12 years old[1]	N/A	Resolved upon discontinuation[1]	N/A

Main characteristics of hepatic injury	Timing	Incidence/prevalence	Predictive Factors	Actionable Reccomendations	Outcomes & management	Emerging biomarkers
had to discontinue treatment due to of liver-related adverse events; no reports of clinically apparent liver injury associated with RUF, but limited use.[1] Reported cases of multi-organ hypersensitivity reactions, one with severe hepatitis[1,2]	treatment initiation[1]	hepatotoxicity[12] but high reporting odds ratio for SJS.[14]	Children younger than 12 years old[1]	N/A	Resolved upon discontinuation[1]	N/A
Stiripentol (STP): Routine hepatic function monitoring[2] is not recommended but the EMA recommends assessing liver function at baseline and every 6 months[3]				**LiverTox likelihood score (A, high; E, low)[1] : E**		
Increases in GGT[1] Low rates of ALT and ALP elevations[1] Fulminant hepatitis, liver injury, acute hepatic failure; hyperammonemic encephalopathy[64]		GGT elevations: Up to 38% of cases.[1] 5 recently reported cases of hyperammonemic encephalopathy, 4 fulminant hepatitis, 4 liver injury, 3 hepatotoxicity, 5 hyperammonemia, reported in children aged 3-11 years[64]	Addition of STP to chronic CLB therapy was not associated with increased frequency of serum aminotransferase elevations, and there were no instances of clinically apparent liver injury[1]	A recommendation is available in EMA labelling: In the event of abnormal liver function test findings, the clinical decision for continuing use or adjusting STP dose in conjunction with adjusting the doses of CLB and VPA needs to be made on an individual patient basis taking into consideration the potential clinical benefits and risks.[3]	N/A	N/A
Tiagabine (TGB): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : E**		
Serum aminotransferase elevations, clinically apparent liver injury, hypersensitivity syndromes or autoimmunity not reported, but use has been limited[1]	N/A	In a pharmacovigilance study, no reports of hepatotoxicity[12]	N/A	N/A	N/A	N/A
Topiramate (TPM) Topiramate Valproate Combination: Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : C**		
Elevations in serum AST and ALP levels during long-term treatment[1,2]	Time to Reye's-like syndrome	AST: 1% (50 mg/day), 3% (400 mg/day); ALP: 3%.[1,2] Increased odds	Risk increases with dose and concurrent VPA treatment[2]	TPM should be discontinued at the first sign of a rash, unless the rash is clearly not drug related. If signs or symptoms	Hepatotoxicity usually rapidly reversible -	N/A

Main characteristics of hepatic injury	Timing	Incidence/prevalence	Predictive Factors	Actionable Reccomendations	Outcomes & management	Emerging biomarkers
May trigger an acute Reye's syndrome-like illness with hyperammonemia, lactic acidosis, and severe hepatic dysfunction; may lead to hepatic failure and hepatitis; cases with lactic acidosis and hyperammonemia may be caused by mitochondrial dysfunction.[1,2] NOTE: TPM may increase the hepatotoxicity risk of VPA or other ASM[1] (see VPA)	~2 months[1]	ratio for GGT elevations in the elderly[33] Hyperammonemia incidence in patients 12 to 17 years of age treated for migraine 26% (100 mg/day) and 14% (50 mg/day) compared to 9% in the placebo group.[2] Acute Reye's syndrome-like illness is rare.[1] In pediatric patients, TPM was the third most commonly-reported ASM in association with DILI.[30] In veterans, 0.4 hospitalizations for severe DILI per 10,000 person-years (95% CI, 0.1-1.3)[13]	Patients with inborn errors of metabolism or reduced hepatic mitochondrial activity face higher TPM hyperammonemia risk, with or without encephalopathy[2]. Acute hepatic failure and hyperammonemia were more common in boys under 18[30], while hyperammonemia was more frequent in elderly males (≥75)[33].	suggest SJS/TEN, use of this drug should not be resumed and alternative therapy should be considered[2] Hyperammonemia/encephalopathy: measure ammonia if encephalopathic symptoms occur (unexplained lethargy, vomiting or changes in mental status)[2]	within a few days of TPM or other drugs being stopped[1]	
Serious skin reactions (SJS/TEN)[2,41]		Rare[14,41]	N/A			
Dose-related hyperammonemia seen in pediatric patients 1 to 24 months treated with TPM and concomitant VPA for partial-onset epilepsy (pharmacokinetic interaction unlikely).[2] May also develop in adults.[65] Lethargy, weakness with marked serum aminotransferase elevations and hyperammonemia; features suggestive of Reye's syndrome[1]	Within 2 to 3 weeks of the addition (or dose increase) of TPM to long-term VPA therapy[1]	1% for TPM-VPA combinations[1]. In one pharmacovigilance study, the second most frequently reported ASM combination associated with DILI in pediatric patients.[30]	In many instances, TPM-VPA DILI is preceded by an acute viral illness[1]		In a case report, DILI associated with a TPM-VPA combination resolved after discontinuation of TPM and down-titration of VPA[65]	

Main characteristics of hepatic injury	Timing	Incidence/prevalence	Predictive Factors	Actionable Reccomendations	Outcomes & management	Emerging biomarkers
Valproic Acid (VPA) and its derivatives: Valproic Acid, Sodium Valproate, and Divalproex Sodium: Routine hepatic function monitoring[2] is recommended.				**LiverTox likelihood score (A, high; E, low)[1] : A**		
ALT elevations, usually asymptomatic.[1] See CBD for additional information on VPA-CBD combinations	During long-term therapy[1]	10-15%[1]	N/A	Boxed warning. VPA should not be administered to patients with hepatic disease or significant hepatic dysfunction; VPA is contraindicated in patients known to have mitochondrial disorders caused by DNA polymerase γ (POLG) mutations and children under 2 years of age who are clinically suspected of having a mitochondrial disorder, and in patients with known urea cycle disorders; when VPA is used in children under the age of 2 years, it should be used with extreme caution and as a sole agent; in patients older than 2 years of age who are clinically suspected of having a hereditary mitochondrial disease, VPA should only be used after other ASMs have failed, and these patients should be closely monitored during treatment for the development of acute liver injury with regular clinical assessments and serum liver test monitoring; POLG mutation screening should be performed in accordance with current clinical practice; caution when administering VPA products to patients with a prior history of hepatic disease; serum liver tests should be performed prior to therapy and at frequent intervals after therapy onset, especially during the first 6 months of treatment. NOTE: serum biochemistry may not be abnormal.[1,2] Prior to the initiation of VPA therapy, evaluation for urea cycle disease should be considered in patient populations described in the FDA labels of VPA products. Patients who develop symptoms of unexplained hyperammonemic encephalopathy while receiving VPA should receive prompt treatment (including discontinuation of VPA) and be evaluated for underlying urea	Can resolve even with continuation of VPA[4]	New dosing recommendation suggested for children <10 years of age based on PBPK modelling (including the ontogeny of VPA metabolism);[66] lower hyperammonemia risk in children when dosage adjusted based on CYP2C9 genotyping;[67] metabolomic profiles indicative of VPA-hepatotoxicity and altered bile acid profiles[68,69]

Main characteristics of hepatic injury	Timing	Incidence/prevalence	Predictive Factors	Actionable Reccomendations	Outcomes & management	Emerging biomarkers
				cycle disorders[2]. VPA should be discontinued immediately in the presence of significant hepatic dysfunction, suspected or apparent.[2]		
Hyperammonemia with minimal or no hepatic injury. Manifested as progressive and episodic confusion, then obtundation and coma (hyperammonemic encephalopathy); elevations in serum ammonia with normal (or near normal) aminotransferase and bilirubin; normal or minimally high VPA levels; likely related to VPA effects on hepatic mitochondrial function[1]	Usually within weeks of starting VPA or dose increases, but can begin after months or years[1]	Hyperammonemia: ~40% of VPA-treated pediatric patients.[70] Hyperammonemic encephalopathy is rare[71]	Risk increases with young age (≤3 years), female gender, carbonic anhydrase inhibitors, concomminant use of strong enzyme inducers, and higher VPA doses.		Resolves within days of stopping the drug.[1] Treatment includes lactulose or intermittent hemodialysis based on severity[72]. Carnitine supplementation may aid recovery.[1]	
Acute hepatocellular injury with jaundice;[1] preceded by non-specific symptoms (e.g., malaise, weakness, lethargy, facial edema, anorexia, and vomiting; might also present with loss of seizure control); [1,2] typically with hepatocellular or mixed enzyme elevation pattern; despite the disease severity, serum aminotransferase levels may not be markedly elevated; hypersensitivity features are rare; in histology, microvesicular steatosis with central lobular necrosis, mild-moderate inflammation and cholestasis. When injury is prolonged, also severe fibrosis, bile duct proliferation and regenerative nodules; mitochondrial toxicity with low carnitine levels[2,34]	Onset usually within 1 to 6 months of starting VPA[1,2]	Fifth most common drug associated with DILI among liver transplant recipients in the US between 1990-2002;[61] estimated risk for fatal VPA-hepatotoxicity in patients less than 2 years old receiving VPA as polytherapy is approximately 1 in 600. Overall risk of fatal hepatotoxicity is 1:37,000[74] In veterans, 0.6 hospitalizations for severe DILI per 10,000 person-years (95% CI, 0.3-1.4)[13]	Higher DILI risk in children under 10, with highest fatality risk under 2.[75] POLG mutations, with or without Alpers-Huttenlocher syndrome, often fatal and poorly responsive to liver transplant.[1,2,76] Increased risk with enzyme-inducing ASMs[77], metabolic disorders, severe seizures with intellectual disability, organic brain disease[1,2], or status epilepticus.[4]		Multiple cases of fatal acute hepatic failure; VPA should be discontinued promptly in the presence of significant hepatic dysfunction, suspected or apparent.[1,2] Carnitine may be used to improve the course of VPA hepatotoxicity.[75] It has been suggested that in individuals whose hepatic enzymes increase to >3 x	

Main characteristics of hepatic injury	Timing	Incidence/prevalence	Predictive Factors	Actionable Reccomendations	Outcomes & management	Emerging biomarkers
					ULN, VPA should be discontinued[4]	
Reye-like syndrome; fever and lethargy, then stupor and coma; elevated ammonia and ALT levels, normal or minimally elevated bilirubin levels; often metabolic acidosis; microvesicular steatosis with inflammation and cholestasis[1] Cases of SJS, but with no causal association with VPA.[73] VPA is generally a safe alternative in patients who developed the ASM hypersensitivity syndrome following treatment with aromatic ASMs.[1] See LTG for additional information on VPA-LTG combinations		SJS/TEN cases are rare[2]	Reye syndrome has been described in children, in association with viral (influenza or varicella) infection[1]			
Vigabatrin (VGB): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : D**		
Isolated case reports of severe liver injury and hepatitis (the drug is rarely used); largely hepatocellular.[1] NOTE: VGB causes marked decrease in ALT and AST plasma activity in up to 90% of patients[1,2]	3 to 10 months after treatment onset[1]	Hepatotoxicity is rare.[1] In a pharmacovigilance study, no reports of hepatotoxicity[12]	N/A	ALT and AST are not reliable markers for detecting early hepatic injury[2]	One case resulted in rapid death from liver failure; another worsened despite stopping VGB, the patient was treated with prednisone and azathioprine and recovered[1]	N/A
Zonisamide (ZNS): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : D**		
Mild increases in serum ALT, AST, ALP, GGT and bilirubin levels,	3-8 weeks after	Rare.[1] In one pharmacovigilance	Suggested hypersensitivity cross-reactivity with other	If a hepatic event is suspected, liver function should be evaluated and	Complete recovery in most	Cases of hypersensitivity

Main characteristics of hepatic injury	Timing	Incidence/prevalence	Predictive Factors	Actionable Reccomendations	Outcomes & management	Emerging biomarkers
without any consistent pattern in the observations of values above the upper limit of normal.[3] Rarely clinically apparent hepatotoxicity, but causality unclear because patients were treated with drug combinations. A single case report of cholestatic hepatitis associated with vanishing bile duct syndrome that ultimately resolved; cases of DRESS or SJS with mild liver test abnormalities[1]	treatment onset[1]	study, no increase in an odds ratio of hepatotoxicity.[12] In another, increased risk of GGT elevations in the elderly.[33] High odds ratio for SJS[14]	non-ASM sulphonamides (e.g., sulfa-based antibiotics), but lack of clinical data to support this observation[78]	discontinuation of ZNS should be considered.[3] ZNS should be discontinued at first sign of a rash or other hypersensitivity signs (fatalities have occurred due to sulphonamide-hypersensitivity reactions, including fulminant hepatic necrosis)[78] #	patients, with persistent liver test abnormalities in at least one patient.[1] #	to ZNS in Japanese patients have been linked to HLA-A*02:07[79]

DRUGS USED FOR ACUTE TREATMENT

Main characteristics of hepatic injury	Timing	Incidence/prevalence	Predictive Factors	Actionable Reccomendations	Outcomes & management	Emerging biomarkers
Diazepam (DZP): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1]** : E (IV); D (Oral)		
No reports on serum enzyme elevations or clinically apparent liver injury with IV treatment, even with prolonged use. However, oral DZP linked to rare instances serum ALT elevations and cholestatic or mixed liver injury[1] NOTE: The label of the buccal film preparation warns about risk of serious adverse reactions including hepatic failure in infants due to benzyl alcohol preservative. The preparation is not approved for use in neonates or infants[2]	4 to 12 weeks of treatment with oral DZP[1]	Rare.[1] Reporting odds ratio for DILI vs. all non-ASM reports, 1.53[12]	No information about cross-reactivity with other benzodiazepines[1]	N/A	Complete recovery without evidence of residual or chronic injury (oral DZP)[1]	N/A

Main characteristics of hepatic injury	Timing	Incidence/prevalence	Predictive Factors	Actionable Reccomendations	Outcomes & management	Emerging biomarkers
Midazolam (MDZ): Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : E**		
Rare serum ALT or ALP elevations; no reports on clinically apparent liver injury[1]	N/A	Rare[1]	No information about cross-reactivity with other benzodiazepines[1]	N/A	N/A	N/A
Lorazepam: Routine hepatic function monitoring[2] is not recommended.				**LiverTox likelihood score (A, high; E, low)[1] : D**		
Rare serum ALT or ALP elevations; extremely rare clinically apparent liver injury; single case report of self-limited cholestatic hepatitis; no cases of acute liver failure or chronic liver injury[1]	Latency of 9 months[1]	Rare[1]	No information about cross-reactivity with other benzodiazepines[1]	As with all benzodiazepines, the use of lorazepam may worsen hepatic encephalopathy; therefore, lorazepam should be used with caution in patients with severe hepatic insufficiency and/or encephalopathy[2]	Complete recovery upon discontinuation[1]	N/A

ABBREVIATIONS

ALP: alkaline phosphatase; **ALT:** alanine aminotransferase; **AST:** aspartate aminotransferase; **DRESS:** Drug Rash with Eosinophilia and Systemic Symptoms; **EMA:** European Medicines Agency; **FAERS:** FDA Adverse Event Reporting System; **GGT:** Gamma-glutamyltransferase; **HBsAg:** hepatitis B surface antigen; **HL:** hemophagocytolytic lymphohistiocytosis; **N/A:** not available; **PBPK:** physiologically-based pharmacokinetic; **ROR:** reporting odds ratio; **SCAR:** severe cutaneous adverse reaction; **ULN:** upper limit of normal. **SJS:** Stevens-Johnson Syndrome.

[#]Important ways to manage DRESS are early recognition, discontinuation of the offending agent as soon as possible (in the absence of an alternative etiology), supportive care, and/or other interventions commonly used to treat DRESS such as systemic corticosteroids.[2]

CATEGORIES OF LIVERTOX'S LIKELIHOOD SCORE[1]

Category A	The drug is well known, well described and well reported to cause either direct or idiosyncratic liver injury and has a characteristic signature; more than 50 cases including case series have been described.
Category B	The drug is reported and known or highly likely to cause idiosyncratic liver injury and has a characteristic signature; between 12 and 50 cases including small case series have been described.
Category C	The drug is probably linked to idiosyncratic liver injury but has been reported uncommonly and no characteristic signature has been identified; the number of identified cases is less than 12 without significant case series.
Category D	Single case reports have appeared implicating the drug, but fewer than 3 cases have been reported in the literature, no characteristic signature has been identified, and the case reports may not have been very convincing. Thus, the agent can only be said to be a possible hepatotoxin and only a rare cause of liver injury.
Category E	Despite extensive use, there is no evidence that the drug has caused liver injury. Single case reports may have been published, but they were largely unconvincing. The agent is not believed to or is unlikely to cause liver injury.
Category E*	The drug is suspected to be capable of causing liver injury or idiosyncratic acute liver injury but there have been no convincing cases in the medical literature. In some situations, cases of acute liver injury have been reported to regulatory agencies or mentioned in large clinical studies of the drug, but the specifics and details supportive of causality assessment are not available. The agent is unproven but suspected of causing liver injury.
Category X	Finally, for medications recently introduced into or rarely used in clinical medicine, there may be inadequate information on the risks of developing liver injury to place it in any of the five categories, and the category is characterized as "unknown."

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