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Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

BENZODIAZEPINE SELECTION IN ALCOHOL WITHDRAWAL TREATMENT: METABOLIC CONSIDERATIONS IN STAGES OF HEPATIC DYSFUNCTION

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SPEAKER DISCLOSURES

✓No conflicts of interest to disclose

The following series planners have no relevant conflicts of interest to disclose; other disclosures have been mitigated.

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OBJECTIVES

1. Recognize the impact that alcohol use has on healthcare expenditures and the possible sequelae of alcohol use on health.
2. Understand the biological process of progressive hepatic dysfunction and the impact on medication metabolism.
3. Appreciate the differences in benzodiazepine metabolism and the ways to assess hepatic function

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ALCOHOL USE DISORDER PREVALENCE AND IMPACT

Disordered alcohol consumption has been increasing steadily over time

Hospitalization is often necessary to manage acute withdrawal/detoxification

Recent estimates indicate that alcohol use disorder generates over $10.1 billion in costs to employer-sponsored insurance in the US [1]

Estimated aggregate cost of hospitalization for alcohol use disorder is $19.8 billion [2]

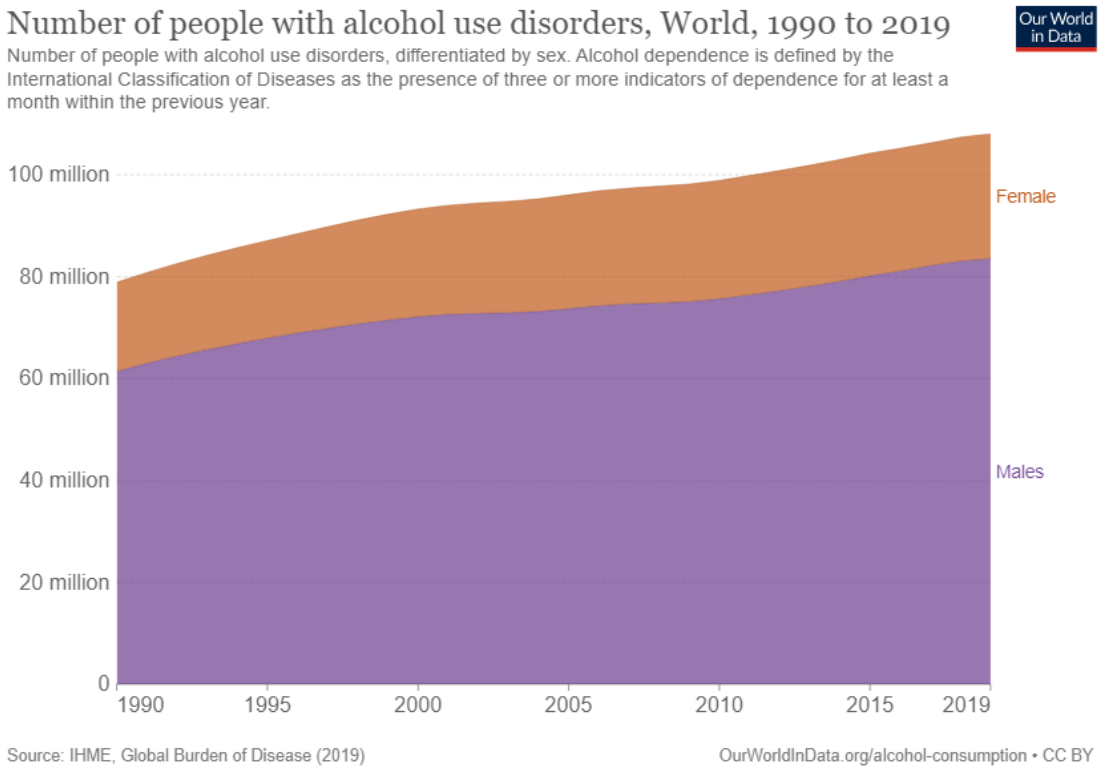

Image from: https://ourworldindata.org/alcohol-consumption

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SEQUELAE OF CHRONIC ALCOHOL USE

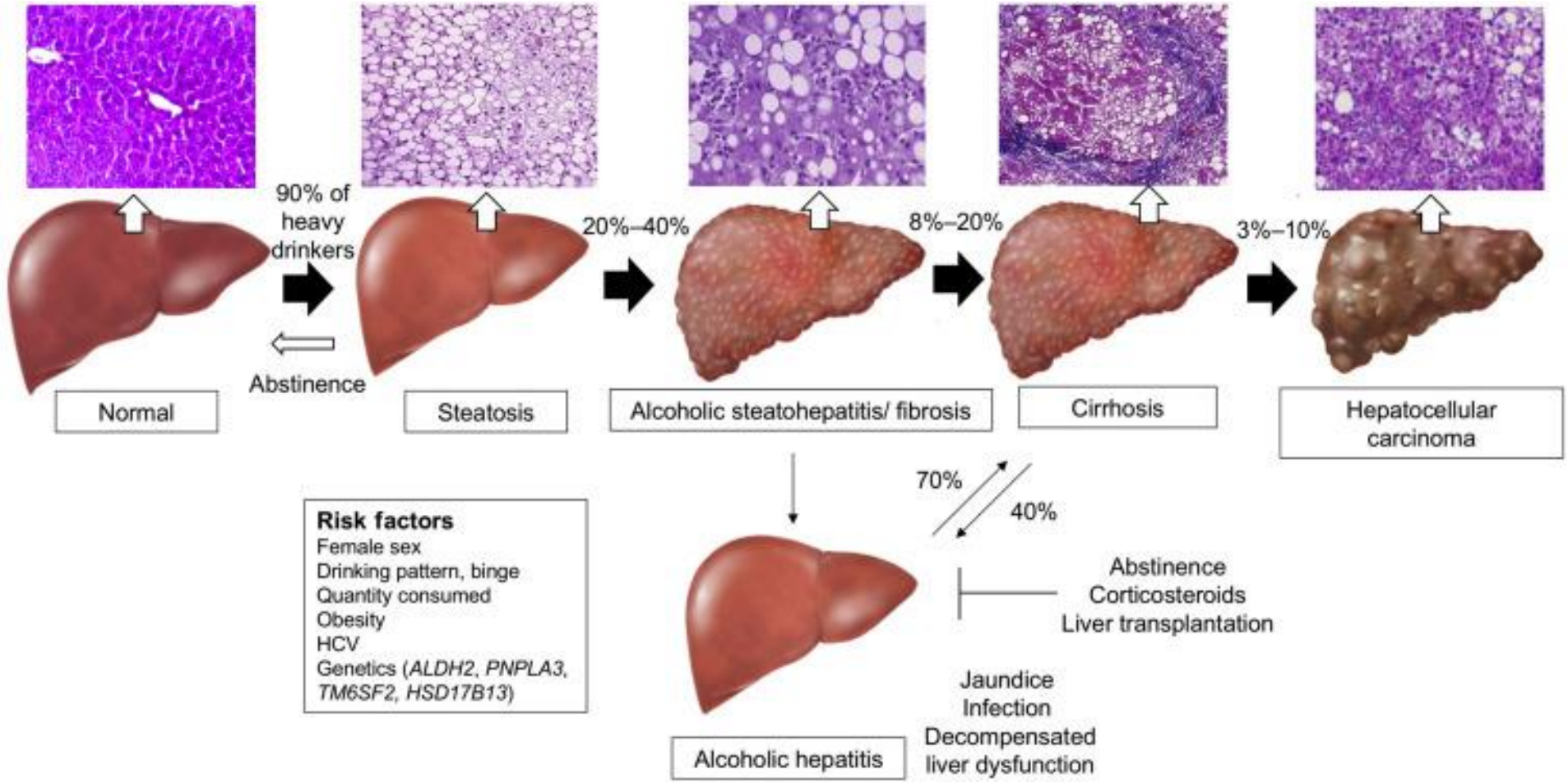

Image from: Ohashi, K., Pimienta, M., & Seki, E. (2018). Alcoholic liver disease: A current molecular and clinical perspective. Liver research, 2(4), 161-172.

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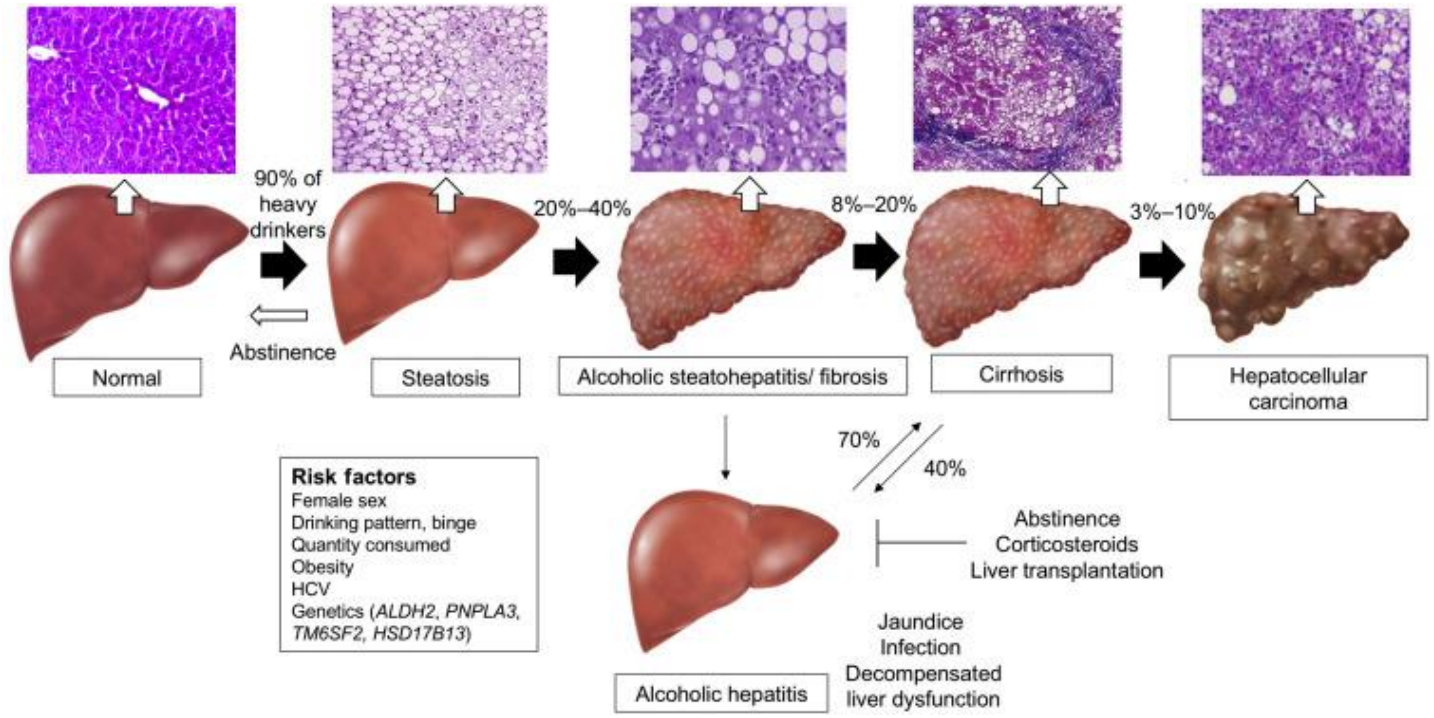
Chronic alcohol consumption promotes lipogenesis of the liver via inhibition of triglyceride and fatty acid oxidation

Accumulation of neutrophils and macrophages within the liver occurs after a cascade of events mediated by the translocation of endotoxins in the form of lipopolysaccharides

Fibrosis begins at the perivenular region, extending to neighboring central or portal regions eventually leading to cirrhosis [3]



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BENZODIAZEPINE METABOLISM

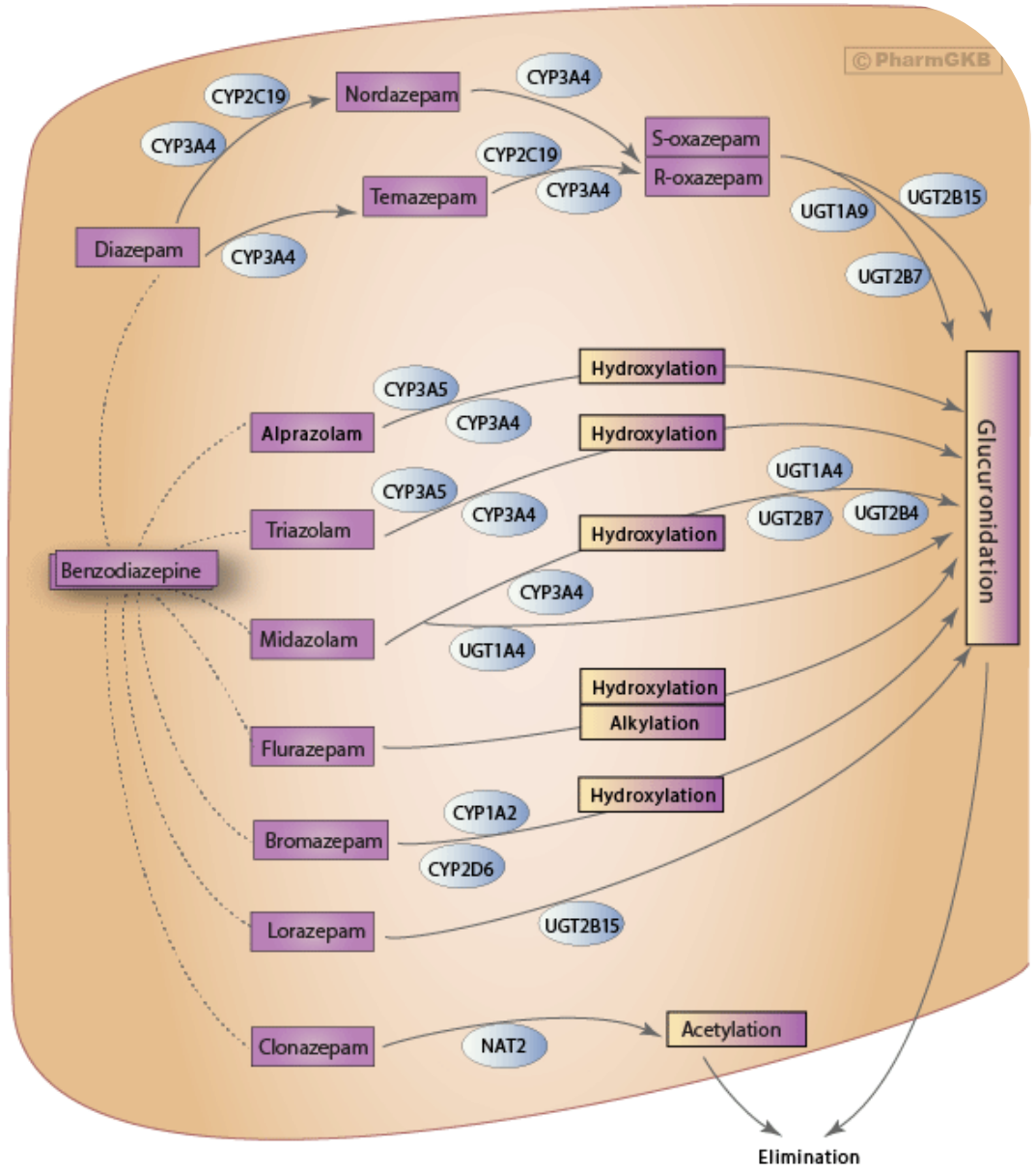

Image from: https://www.pharmgkb.org/pathway/PA165111375

- Commonly used benzodiazepines in alcohol withdrawal treatment:
  - Chlordiazepoxide: t½ 5-30 hours, time to peak: 0.5-2 hours, metabolized by CYP3A4 and CYP2C19 [4]

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BENZODIAZEPINE METABOLISM

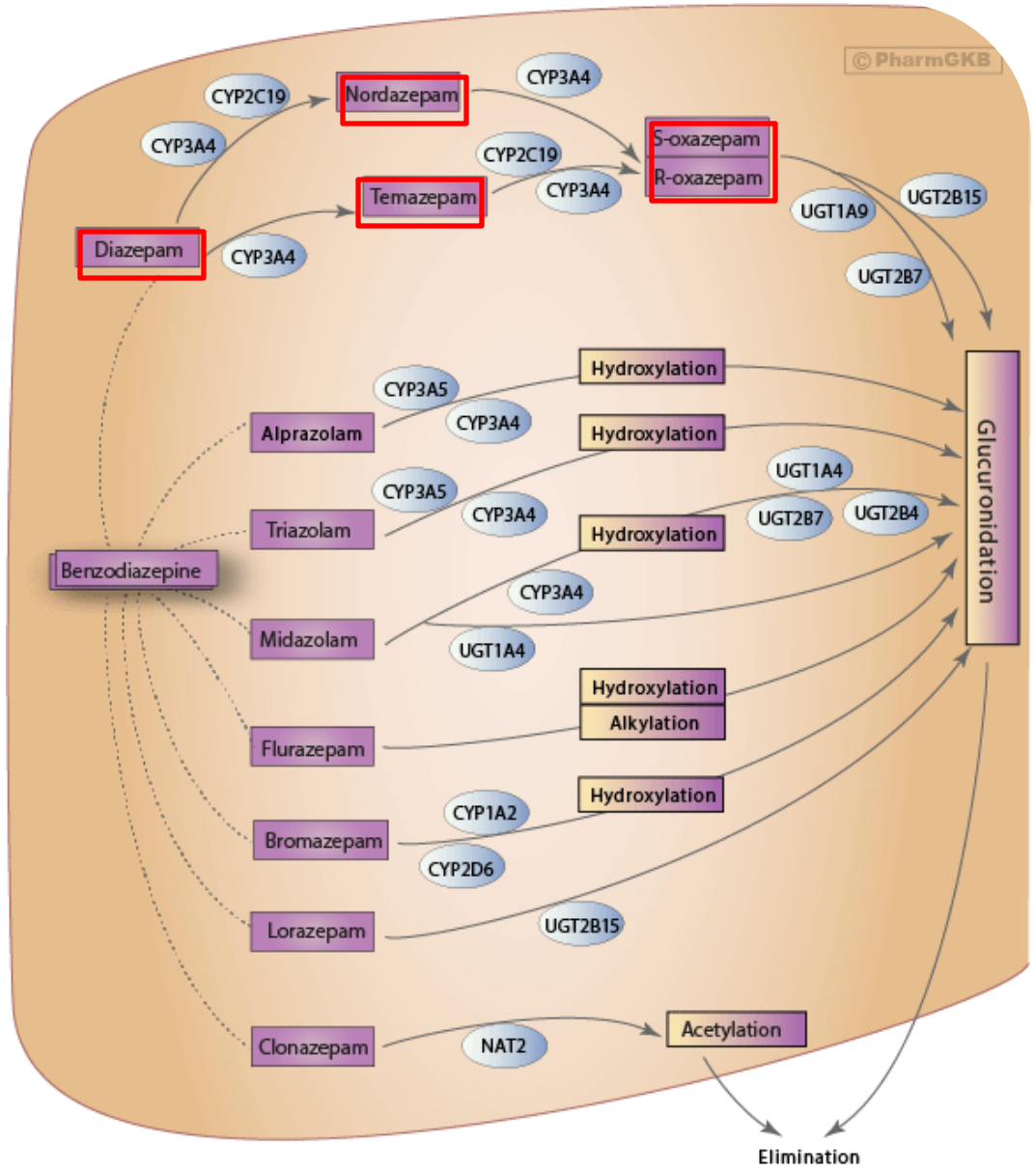

Image from: https://www.pharmgkb.org/pathway/PA165111375

- Commonly used benzodiazepines in alcohol withdrawal treatment:
  - Diazepam: t½ PO: 44-48 hours; IV: 33-45 hours; IM: ~60-72 hours, time to peak: IV: 5 mins; IM: 0.25-2 hours; PO: 0.25-2.5 hours (1.25 hours when fasting; 2.5 hours with food), metabolized by CYP3A4 and CYP2C19 [5]

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BENZODIAZEPINE METABOLISM

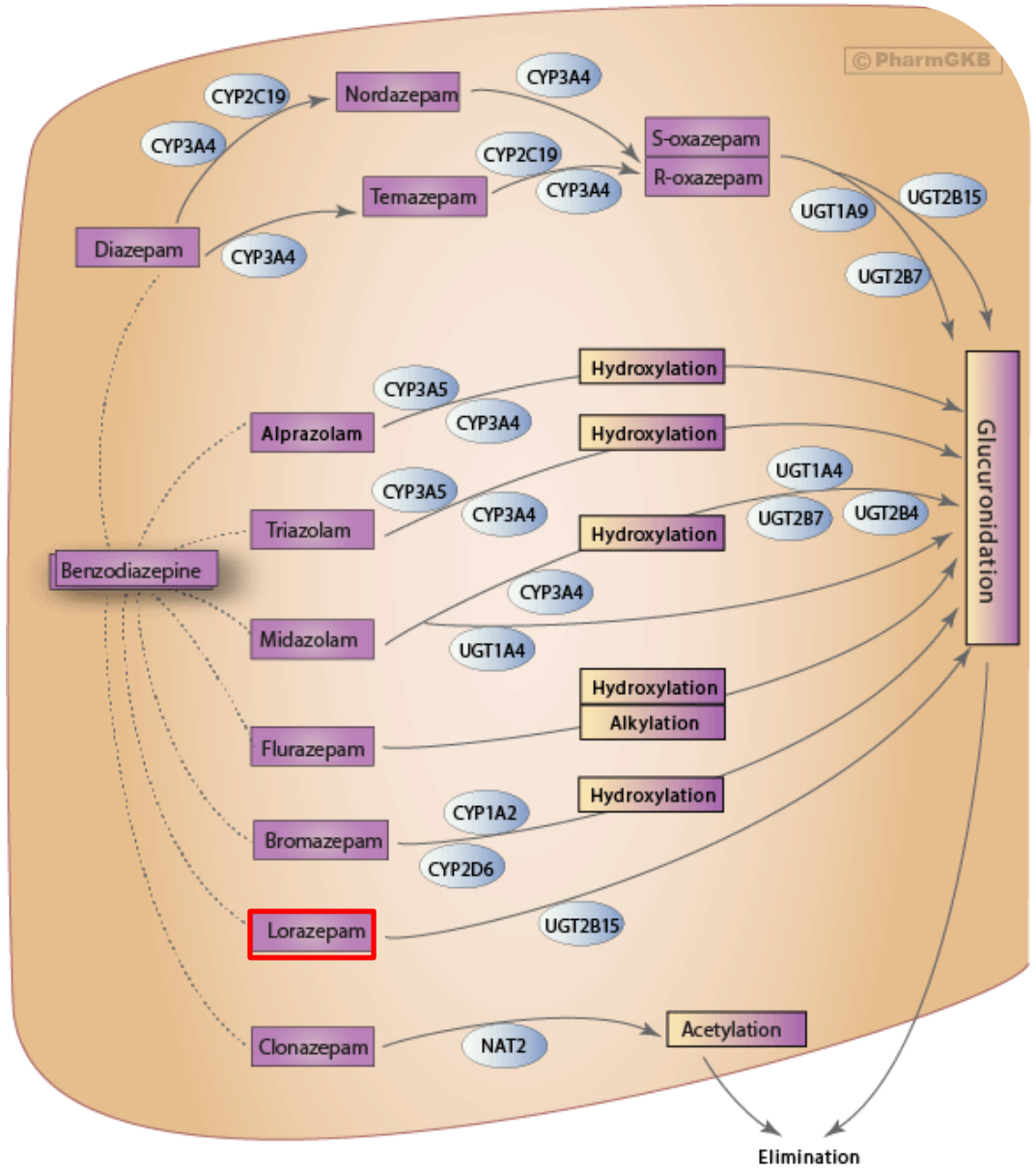

Image from: https://www.pharmgkb.org/pathway/PA165111375

- Commonly used benzodiazepines in alcohol withdrawal treatment:
  - Lorazepam: t½ PO: ~12 hours; IV: ~14 hours; IM: ~13-18 hours, time to peak: PO 2 hours and IV 30 minutes, metabolized via glucuronidation

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BENZODIAZEPINE METABOLISM

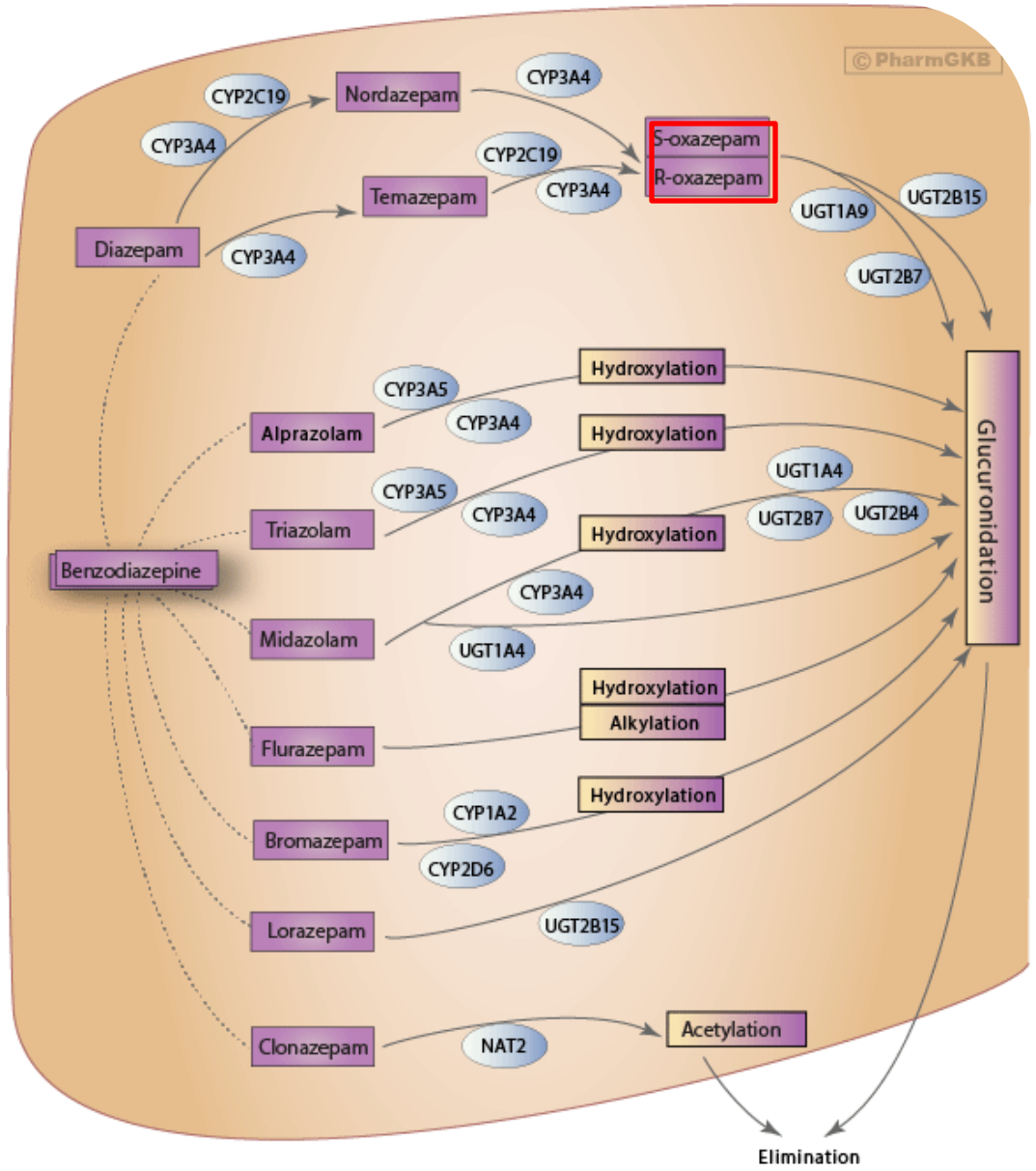

Image from: https://www.pharmgkb.org/pathway/PA165111375

- Commonly used benzodiazepines in alcohol withdrawal treatment:
  - Oxazepam: t½ 6-11 hours, time to peak: 3 hours, metabolized via glucuronidation

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METHODOLOGY FOR ASSESSING HEPATIC FUNCTION

Many clinicians utilize AST and ALT as a proxy for hepatic function

- Most FDA data relies upon Child-Pugh classification for assessing impact of liver disease on medication metabolism
- MELD, MELD-Na, and MELD 3.0 scores are sometimes used to determine hepatic function
- Gamma-glutamyl transferase (GGT) rises with hepatic enzyme induction due to chronic alcohol use

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	**Points***		
	1	2	3
Encephalopathy	None	Mild to moderate (grade 1 or 2)	Severe (grade 3 or 4)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3
***Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)**			
Class A = 5 to 6 points (least severe liver disease)			
Class B = 7 to 9 points (moderately severe liver disease)			
Class C = 10 to 15 points (most severe liver disease)			

Image from: https://www.hepatitisc.uw.edu/go/key-populations-situations/treatment-cirrhosis/core-concept/all

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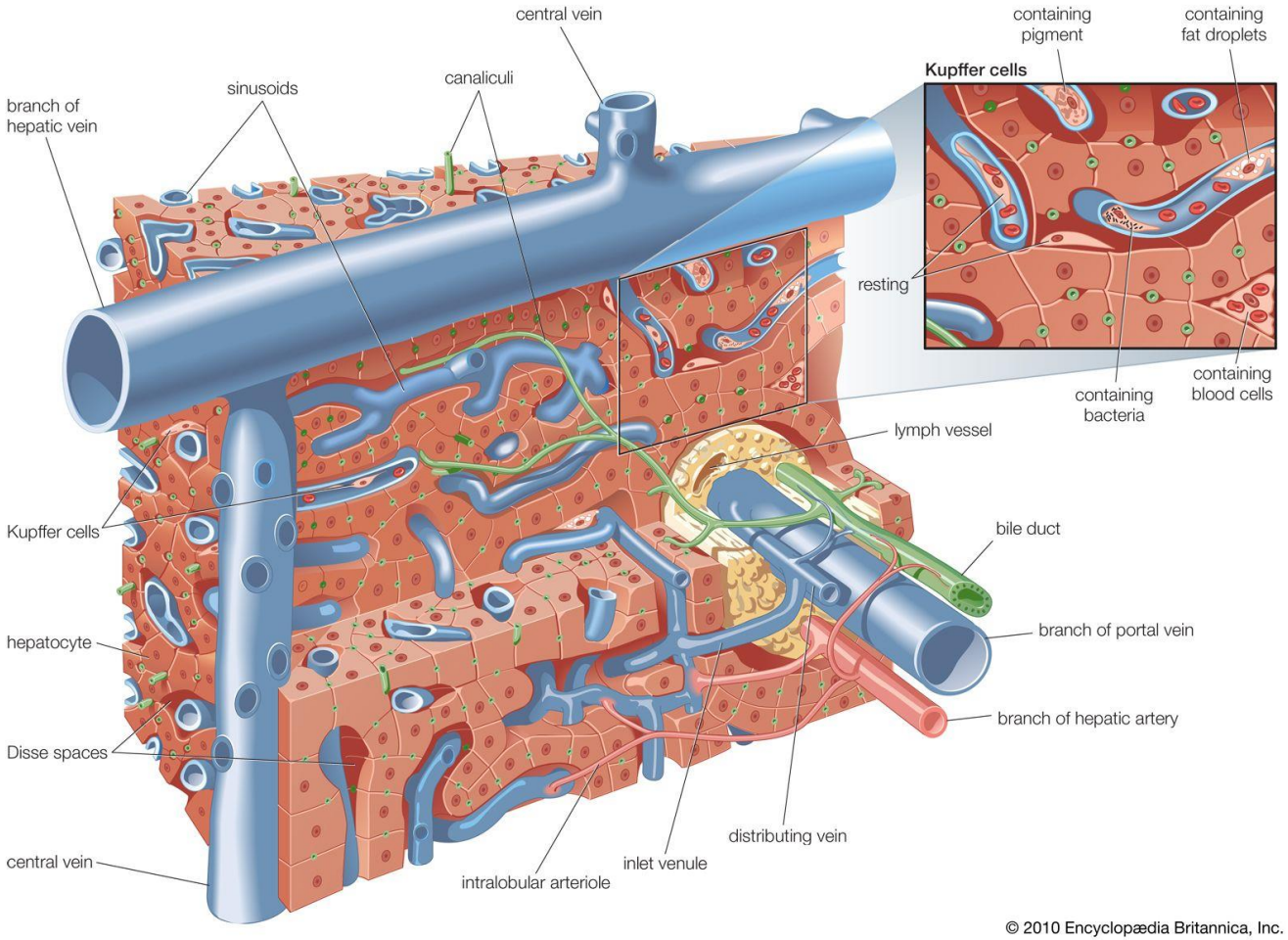
THEORIES OF ALTERED HEPATIC METABOLISM

The current proposed mechanisms underlying altered hepatic drug metabolism in liver disease:

- Intact hepatocyte theory
- Sick cell theory
- Impaired drug uptake theory
- Oxygen limitation theory



https://cdn.britannica.com/09/70109-050-DF278240/liver-Liver-cells-structure-hepatocytes-access-Kupffer.jpg

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SUMMARY AND RECOMMENDATIONS

AUD is associated with high healthcare costs

By utilizing appropriate management of alcohol withdrawal syndromes, there is a lower likelihood of ICU admissions and higher healthcare costs

Chronic alcohol use can lead to hepatic metabolism impairments

Alcoholic steatosis can develop into alcoholic steatohepatitis and alcoholic hepatitis, which is associated with increased fibrosis and eventually cirrhosis

Benzodiazepines are metabolized by CYP450 enzymes and glucuronidation

CYP3A4 and 2C19 are primarily implicated with metabolites or active drugs undergoing glucuronidation prior to elimination

Cirrhosis and alcoholic hepatitis impair metabolism

In the absence of demonstrable hepatic dysfunction, it is not necessary to avoid specific benzodiazepines

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REFERENCES

- Gryczynski, J., Schwartz, R. P., O'Grady, K. E., Restivo, L., Mitchell, S. G., & Jaffe, J. H. (2016). Understanding patterns of high-cost health care use across different substance user groups. Health Affairs, 35(1), 12-19.
- Hall, P., & Cash, J. (2012). What is the real function of the liver 'function' tests?. The Ulster medical journal, 81(1), 30–36.
- Li, M., Peterson, C., Xu, L., Mikosz, C. A., & Luo, F. (2023). Medical costs of substance use disorders in the US employer-sponsored insurance population. JAMA network open, 6(1), e2252378-e2252378.
- Morgan, D. J., & McLean, A. J. (1995). Clinical pharmacokinetic and pharmacodynamic considerations in patients with liver disease: an update. Clinical pharmacokinetics, 29, 370-391.
- SAMHSA, Center for Behavioral Health Statistics and Quality. 2021 National Survey on Drug Use and Health. Table 5.6A—Alcohol use disorder in past year: among people aged 12 or older; by age group and demographic characteristics, numbers in thousands, 2021. https://www.samhsa.gov/data/sites/default/files/reports/rpt39441/NSDUHDetailedTabs2021/NSDUHDetailedTabs2021/NSDUHDetTabsSect5pe2021.htm#tab5.6a
- Shah NJ, Royer A, John S. Alcoholic Hepatitis. [Updated 2023 Jun 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470217
- Talal, A.H., Venuto, C.S. and Younis, I. (2017), Assessment of Hepatic Impairment and Implications for Pharmacokinetics of Substance Use Treatment. Clinical Pharmacology in Drug Development, 6: 206-212. https://doi.org/10.1002/cpdd.336
- Weintraub S. J. (2017). Diazepam in the Treatment of Moderate to Severe Alcohol Withdrawal. CNS drugs, 31(2), 87–95. https://doi.org/10.1007/s40263-016-0403-y

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