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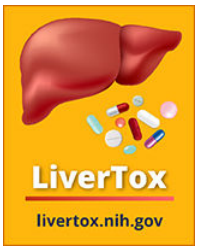

Opioids

Updated: November 24, 2020.

OVERVIEW

Introduction

The opioids are a large class of medications related in structure to the natural plant alkaloids found in opium that are derived from the resin of the opium poppy, Papaver somniferum. The natural alkaloids are also referred to as opiates and include morphine and codeine. Synthetic derivatives include heroin, fentanyl, hydromorphone, methadone, buprenorphine and others. The opioids are highly potent and effective analgesics, but most have a high potential for dependency and abuse.

Opioids act by engagement of specific cell surface receptors; the opiate receptors, which are designated μ [mu], κ [kappa] and δ [delta]. These receptors are found predominantly in the central nervous system, brain and spinal column, but are also present on vascular, cardiac, lung, gut and even peripheral blood mononuclear cells. Engagement of the opiate receptors generates a series of intracellular signals, including inhibition of adenylate cyclase, decreased opening of calcium channels, increased potassium currents and activation of protein kinase C (PKC). The major effect of these pathways is reduction in cell excitability and neurotransmission. The natural ligands for the opiate receptors are the so-called endogenous opioid peptides such as the enkephalins, endorphins and endomorphins.

The opioids have a variety of clinical effects, but are predominantly known and used for their profound pain relieving effects. Other effects that are often linked to opiate analgesia include euphoria, changes in mood, drowsiness and mental clouding. However, the distinctive feature of the analgesia induced by the opioids is the lack of loss of consciousness. The pain is often described as less intense, but still present although better tolerated. Thus, the opioids do not decrease or treat the cause of the painful stimulus, but rather decrease its perception.

Other effects of opioids include respiratory depression, decreased gastrointestinal motility, sedation, nausea, vomiting, constipation and intestinal bloating. Opioids also have direct cardiovascular effects, decreasing blood pressure, causing vasodilation and decreasing cardiac work.

Most opioids have similar effects and side effects, although pharmacokinetic differences, tissue distribution, and receptor type specificity probably account for the variation in effects of the various synthetic and semisynthetic derivatives of morphine. Morphine is considered the prototype opiate, against which other agents are measured for their analgesic effects as well as adverse side effects.

The opioids can be categorized into subclasses on the basis of their chemical structure as opium alkaloids (opiates: codeine, morphine), semisynthetic derivatives of the natural alkaloids (hydrocodone, hydromorphone, oxycodone, buprenorphine), and various classes of synthetic opioids such as the anililopiperidines (fentanyl,

alfentanil, sufentanil, remifentanil), diphenylpropylamine derivatives (propoxyphene, dextropropoxyphene, methadone, diphenoxylate, loperamide), and others (pentazocine, butorphanol, nalbuphine, levorphanol, tramadol), and, the opioid antagonists (nalmefene, naloxone and naltrexone). They can also be informally classified based upon their major use such as anesthesia (fentanyl, alfentanil, remifentanil, sufentanil), severe pain (morphine, hydromorphone, levorphanol, meperidine), moderate-to-severe acute or chronic pain (transdermal or transbuccal fentanyl, codeine, oxycodone, hydrocodone, levorphanol, methadone), diarrhea (loperamide, diphenoxylate), and cough (codeine, hydrocodone). Finally, opioids can be categorized on the basis of their action as full agonists, partial agonists or mixed agonists/antagonists, and antagonists of opiate receptors.

Opioid receptor antagonists are used to reverse the effects of opioids and are invaluable in the management of opioid overdose (naloxone, naltrexone, nalmefene). Specialized opioid antagonists can be used to reverse unwanted opioid effects, such as constipation in patients with chronic pain on long-term opioids. These agents (naldemedine, naloxegol) are generally modified so as not to cross the blood brain and reverse the central nervous system effects of opiates.

Opioids are rare causes of drug induced liver disease and are not mentioned in large case series of clinically apparent liver injury caused by medications. In physiological, pain relieving doses, opioids have not been implicated in causing clinically apparent liver injury, acute liver failure, chronic hepatitis or vanishing bile duct syndrome. However, overdoses of the more potent opioids have been linked to cases of acute liver injury, usually with a precipitous onset and pattern of acute toxicity with marked elevations in serum aminotransferase levels and early onset of signs of hepatic failure. This syndrome has been best characterized after buprenorphine overdose or abuse, but likely occurs with others. It is possible that the implicated opioids are not directly toxic to the liver, but cause ischemic liver injury due to respiratory failure, cardiovascular collapse, shock and anoxia that can occur with severe opioid overdose. The clinical syndrome resembles acute hepatic necrosis and liver failure, but is rapidly reversible and rarely the primary cause of death from overdose.

A special form of liver injury linked to opioid use occurs with their fixed drug combinations with acetaminophen. These combinations are commonly used for moderate to moderately severe pain and can lead to abuse. If taken too frequently, acetaminophen doses may reach toxic levels, particularly with overuse for several days in the face of malnutrition, alcohol abuse or intercurrent illness. These other stresses can lower hepatic glutathione levels and predispose to acetaminophen hepatotoxicity. This constellation of events is referred to as inadvertent or unintended acetaminophen overdose or more colloquially as a “therapeutic misadventure”. Because of their potential for hepatotoxicity, opioid combinations in which the dose of acetaminophen is greater than 325 mg per tablet or capsule were discontinued.

References to the safety and hepatotoxic potential of the various opiate agonists are given together at the end of this overview section. References to the opioids and the opiate antagonists used to treat substance abuse are given separately with each agent (buprenorphine, methadone, nalmefene, naloxone, naltrexone). The opioids are discussed individually or as groups of agents and links to each are given below.

Full and partial agonists:

- Alfentanil
- Buprenorphine
- Butorphanol
- Codeine
- Diphenoxylate
- Fentanyl
- Heroin
- Hydrocodone
- Hydromorphone

- Levorphanol
- Loperamide
- Meperidine
- Methadone
- Morphine
- Opium
- Oxycodone
- Oxymorphone
- Pentazocine
- Remifentanil
- Sufentanil
- Tramadol

Opiate antagonists:

- Naldemedine
- Nalmefene
- Naloxegol
- Naloxone
- Naltrexone

ANNOTATED BIBLIOGRAPHY

References updated: 24 November 2020

Zimmerman HJ. Narcotic analgesics. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999: pp. 710-11.

(Expert review of hepatotoxicity published in 1999 discusses morphine, heroin, methadone and codeine, mentioning that studies in humans "have shown little evidence of hepatic injury").

Larrey D, Ripault MP. Illegal and recreational compounds. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 456-7.

(Review of hepatotoxicity discusses buprenorphine, an orally available morphine analogue, which has been linked to cases of severe acute liver injury, usually as a result of intravenous administration).

Yaksh T, Wallace M. Opioids, analgesia, and pain management. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 355-386.

(Textbook of pharmacology and therapeutics).

Edland JF. Liver disease in heroin addicts. Hum Pathol. 1972;3:75–84. PubMed PMID: 5060682.

(Review of autopsy findings in the liver of heroin addicts mentions the frequency of nonspecific portal inflammation, lymph node enlargement in the porta hepatis, typical changes of viral hepatitis including subacute hepatic necrosis with 3 representative case histories).

Stimmel B, Vernace S, Tobias H. Hepatic dysfunction in heroin addicts. The role of alcohol. JAMA. 1972;222:811–2. PubMed PMID: 4677931.

(Among 46 heroin users admitted for methadone maintenance, 85% admitted to excessive alcohol intake, and 10 of 12 patients with unexplained liver test abnormalities had changes of alcoholic hepatitis on liver biopsy).

Ireton HJ, Gust ID, Moon WJ, Lehmann N, Stening GF, Smallwood RA. The covert liver disease of drug addicts. Aust N Z J Med. 1974;4:444–9. PubMed PMID: 4532912.

(Among 20 injection drug users, 11 [55%] had abnormal liver tests [AST 41-98 U/L] and 19 [95%] had abnormalities on liver biopsy, often being mild; none of the patients had HBsAg in serum).

Gorodetzky CW, Sapira JD, Jasinski DR, Martin WR. Liver disease in narcotic addicts. I. The role of the drug. Clin Pharmacol Ther. 1968;9:720–4. PubMed PMID: 5721975.

(20 male prison inmates were given morphine daily for 6-8 months and then switched to methadone that was slowly withdrawn; monthly testing demonstrated that serum ALT and AST values did not change appreciably during periods of morphine or methadone administration).

Sapira JD, Jasinski DR, Gorodetzky CW. Liver disease in narcotic addicts. II. The role of the needle. Clin Pharmacol Ther. 1968;9:725–39. PubMed PMID: 5721976.

(Among 32 prison inmates with a history of heroin use, 26 [81%] had some clinical or biochemical evidence of liver disease, and the frequency of chronic hepatitis increased with number of years of injection use).

Lapierre J. Possible hepatotoxic effect of methadone. Can Med Assoc J. 1969;101:113. PubMed PMID: 5794138.

(Long term heroin user developed nausea and dizziness within a week of starting methadone with atypical lymphocytosis; liver tests were not done until after stopping methadone and then showed minor abnormalities only [bilirubin normal, ALT 56 U/L, Alk P normal]; no further follow up available).

Tartakow IJ. Narcotic-induced hepatitis. Am J Med. 1971;50:313–6. PubMed PMID: 5553950.

(Among 1015 cases of viral hepatitis reported in one county in NY over a 3 year period, 162 were believed to be serum hepatitis, of which 107 [66%] occurred in injection drug users).

Kreek MJ, Dodes L, Kane S, Knobler J, Martin R. Long-term methadone maintenance therapy: effects on liver function. Ann Intern Med. 1972;77:598–602. PubMed PMID: 4629927.

(Among 214 patients with opioid dependency treated with maintenance methadone therapy for up to 3 years, there were no significant changes in liver tests and no deaths from liver disease).

Seeff LB. Hepatitis in the drug abuser. Med Clin North Am. 1975;59:843–8. PubMed PMID: 1095845.

(Review of the frequency and clinical features of viral hepatitis in injection drug users, including the frequency of chronic hepatitis and history of multiple bouts of hepatitis, only one of which is associated with HBsAg positivity).

Gelb AM, Mildvan D, Stenger RJ. The spectrum and causes of liver diseases in narcotic addicts. Am J Gastroenterol. 1977;67:314–8. PubMed PMID: 879147.

(Among 42 heroin users with liver disease, 79% were also heavy alcohol users and all 17 patients with cirrhosis also abused alcohol, suggesting that alcohol plays a major role in serious liver disease among drug users).

Vandelli C, Piaggi V, Battilani R, Cariani E, Sirotti MA. Relationship between HBV markers and heroin as a cause of liver injury in drug addicts. Drug Alcohol Depend. 1984;14:129–33. PubMed PMID: 6510216.

(Among 50 injection drug users admitted to start methadone maintenance who had liver tests abnormalities and underwent liver biopsy, 36 had chronic active hepatitis, 4 had chronic persistent hepatitis, and 10 had nonspecific reactive changes, and all 23 patients with HBsAg in serum had chronic active hepatitis).

Joehl RJ, Koch KL, Nahrwold DL. Opioid drugs cause bile duct obstruction during hepatobiliary scans. Am J Surg. 1984;147:134–8. PubMed PMID: 6537876.

(32 year old woman with abdominal pain and fever treated with meperidine had an abnormal hepatobiliary scan, but on subsequent laparotomy had a normal biliary system without gallstones; in subsequent volunteer studies, opioid drugs caused delayed clearance of technetium labeled iminodiacetic acid and scans suggested bile duct obstruction).

Bickel WK, Stitzer ML, Bigelow GE, Liebson IA, Jasinski DR, Johnson RE. A clinical trial of buprenorphine: comparison with methadone in the detoxification of heroin addicts. Clin Pharmacol Ther. 1988;43:72–8. PubMed PMID: 3275523.

(Among 45 patients with opioid dependency treated with either buprenorphine or methadone for up to 90 days, no discussion of side effects or ALT levels).

de Araújo MS, Gerard F, Chossegros P, Porto LC, Barlet P, Grimaud JA. Vascular hepatotoxicity related to heroin addiction. Virchows Arch A Pathol Anat Histopathol. 1990;417(6):497–503. PubMed PMID: 2125388.

(Histological analysis of liver biopsies from 39 injection drug users with ALT elevations found sinusoidal dilatation and centro-lobular inflammation were more prominent in actively using compared to previous heroin users, but fibrosis was less).

Drummer OH, Opeskin K, Syrjanen M, Cordner SM. Methadone toxicity causing death in ten subjects starting on a methadone maintenance program. Am J Forensic Med Pathol. 1992;13:346–50. PubMed PMID: 1288269.

(Among patients starting methadone maintenance who died acutely, the cause of death was respiratory depression in 5 patients and, while all ten had chronic hepatitis, liver disease did not appear to be the cause in any).

Thompson DR. Narcotic analgesic effects on the sphincter of Oddi: a review of the data and therapeutic implications in treating pancreatitis. Am J Gastroenterol. 2001;96:1266–72. PubMed PMID: 11316181.

(Systematic review of the literature on the effects of opioids on sphincter of Oddi spasm, found little difference among the various opioids in causing an increase in sphincter pressure or symptomatic pancreatitis; recommending use of morphine for pain management, even in acute pancreatitis).

Economou G, Ward-McQuaid JN. A cross-over comparison of the effect of morphine, pethidine, pentazocine, and phenazocine on biliary pressure. Gut. 1971;12:218–21. PubMed PMID: 4928171.

(Among 31 patients after cholecystectomy with T tubes, morphine, meperidine and pentazocine caused increased bile duct pressure; no mention of abnormal liver tests).

Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. JAMA. 1992;267:2750–5. PubMed PMID: 1578593.

(Trial comparing buprenorphine vs two doses of methadone for opioid dependence for 17 weeks found no serious adverse events in either group; no mention of liver injury or ALT elevations).

Clark RF, Wei EM, Anderson PO. Meperidine: therapeutic use and toxicity. J Emerg Med. 1995;13:797–802. Review. PubMed PMID: 8747629.

(Review of the efficacy and safety of meperidine, a synthetic opioid used in emergency departments; it has variable absorption and bioavailability and toxicities include seizures and neuropsychiatric reactions, making it a second line agent for treatment of severe pain).

Ling W, Wesson DR, Charuvastra C, Klett CJ. A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence. Arch Gen Psychiatry. 1996;53:401–7. PubMed PMID: 8624183.

(Among 225 patients with opioid dependency treated with either buprenorphine or two doses of methadone over a one year period, adverse events were similar in both groups and there were no serious liver related events).

Petry NM, Bickel WK, Piasecki D, Marsch LA, Badger GJ. Elevated liver enzyme levels in opioid-dependent patients with hepatitis treated with buprenorphine. Am J Addict. 2000;9:265–9. PubMed PMID: 11000922.

(Among 120 opioid dependent patients treated with buprenorphine, ALT and AST levels did not change in patients whose levels were normal initially, but increased slightly in those with preexisting abnormalities [median ALT increase=8 U/L]).

Mattick RP, Ali R, White JM, O'Brien S, Wolk S, Danz C. Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. Addiction. 2003;98:441–52. PubMed PMID: 12653814.

(Controlled trial in 405 patients with opioid dependence found similar rates of adverse events with buprenorphine and methadone; one patient had hepatitis C, but no other liver related adverse events reported).

Ho V, Stewart M, Boyd P. Cholestatic hepatitis as a possible new side-effect of oxycodone: a case report. J Med Case Rep. 2008;2:140. PubMed PMID: 18452597.

(A 34 year old man developed jaundice 6 weeks after outpatient surgery and while receiving oxycodone [bilirubin 8.2 mg/dL, ALT 295 U/L, Alk P 358 U/L], having received cephalosporin at the time of surgery, with slow but ultimately complete recovery).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology. 2008;135:1924–34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease collected in the US between 2003 and 2008, no cases were attributed to an opioid analgesic).

Pinto H, Maskrey V, Swift L, Rumball D, Wagle A, Holland R. The SUMMIT trial: a field comparison of buprenorphine versus methadone maintenance treatment. J Subst Abuse Treat. 2010;39:340–52. PubMed PMID: 20817384.

(Patient preference controlled trial comparing buprenorphine and methadone for up to 6 months in 361 opiate dependent subjects; no discussion of hepatotoxicity or ALT elevations).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology. 2010;52:2065–76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none to methadone or other opiates or agents used to treat substance abuse).

Gibson A, Randall D, Degenhardt L. The increasing mortality burden of liver disease among opioid-dependent people: cohort study. Addiction. 2011;106:2186–92. PubMed PMID: 21749525.

(Among 2489 people enrolled in methadone maintenance programs in Australia between 1980 and 1985 who were tracked using the National Death Index, the standardized mortality rate was increased compared to the general population [SMR = 4.6] and 17% of deaths were due to liver disease [SMR 28 for women and 14.5 for men]).

Saxon AJ, Ling W, Hillhouse M, Thomas C, Hasson A, Ang A, Doraimani G, et al. Buprenorphine/Naloxone and methadone effects on laboratory indices of liver health: a randomized trial. Drug Alcohol Depend. 2013;128:71–6. PubMed PMID: 22921476.

(Among 731 patients with opioid dependency treated with either buprenorphine and naloxone vs methadone for at least 24 weeks, 12.6% vs 17.9% developed ALT elevations [>2 times ULN] which were "extreme" in only 2.1% vs 3.6% [bilirubin 0.7-3.7 mg/dL, ALT 418-6280 U/L], usually attributable to underlying HBV or HCV infection).

Drugs for pain. Treat Guidel Med Lett. 2013;11(128):31–42. PubMed PMID: 23518635.

(Concise summary and recommendations for use of analgesics including aspirin, acetaminophen, NSAIDs, opiates and adjuvant pain medications; no mention of liver related adverse events).

Nalamachu S, Rauck RL, Hale ME, Florete OG Jr, Robinson CY, Farr SJ. A long-term, open-label safety study of single-entity hydrocodone bitartrate extended release for the treatment of moderate to severe chronic pain. J Pain Res. 2014;7:669–78. PubMed PMID: 25473308.

(Open label study of 638 patients with chronic pain symptoms treated with extended release hydrocodone in varying doses found a greater than 50% improvement in pain scores in 40% of patients and "no clinically meaningful changes from baseline were observed in blood chemistry").

Lucas GM, Young A, Donnell D, Richardson P, Aramrattana A, Shao Y, Ruan Y, Liu W, et al; HPTN 058 study group. Hepatotoxicity in a 52-week randomized trial of short-term versus long-term treatment with buprenorphine/naloxone in HIV-negative injection opioid users in China and Thailand. Drug Alcohol Depend. 2014;142:139–45. PubMed PMID: 24999060.

(Among 1036 patients with opioid use disorder treated with buprenorphine/naloxone in short [18 day] or long [52 week] courses, serum ALT elevations above 3 times ULN arose in 76 patients [7%], most instances occurring with either acute or chronic HCV infection and rates of ALT elevations were similar with either short and long term use, as well as after discontinuation of the medication).

Naloxegol (Movantik) for opioid-induced constipation. Med Lett Drugs Ther. 2015;57(1478):135–7. PubMed PMID: 26393826.

(Concise review of the mechanism of action, efficacy and safety of naloxegol shortly after its approval for use in the US; mentions dose related gastrointestinal side effects, but not ALT elevations or hepatotoxicity).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology. 2015;148:1340–52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to opiates or opiate antagonists).

Feng G, Luo Q, Guo E, Yao Y, Yang F, Zhang B, Li L. Multiple organ dysfunction syndrome, an unusual complication of heroin intoxication: a case report and review of literature. Int J Clin Exp Pathol. 2015;8:11826–30. PubMed PMID: 26617935.

(32 year old Chinese man was found unconscious after an opioid overdose and developed severe acidosis, respiratory failure and shock with evidence of cardiac, muscle, renal and hepatic injury [bilirubin not given, ALT 61 rising to 330 U/L, CPK 454 U/L, myoglobin 2000 ng/mL], with ultimate recovery, the liver injury most likely due to ischemic hepatitis).

Tetrault JM, Tate JP, Edelman EJ, Gordon AJ, Lo Re V 3rd, Lim JK, Rimland D, et al. Hepatic safety of buprenorphine in HIV-infected and uninfected patients with opioid use disorder: the role of HCV-infection. J Subst Abuse Treat. 2016;68:62–7. PubMed PMID: 27431048.

(Among 666 patients [mostly men] identified in a Veterans Administration electronic medical database who were started on buprenorphine and were monitored, 14 developed "drug-induced liver injury", all of whom had received a potentially hepatotoxic medication [93%] or had preexisting HCV infection [7%], and there was no overall "substantial" change in serum ALT, AST or bilirubin levels).

Pergolizzi JV, Raffa RB, Marcum Z, Colucci S, Ripa SR. Safety of buprenorphine transdermal system in the management of pain in older adults. Postgrad Med. 2017;129:92–101. PubMed PMID: 27929709.

(Review of the literature on the safety and efficacy of buprenorphine in elderly patients mentions that liver abnormalities were rare [<1%] and ALT values above 3 times ULN occurred in 0.2% of both elderly and younger adults).

Ward A, Del Campo M, Hauser K. Complications with oxycodone and naloxone. Aust Prescr. 2017;40:156–7. PubMed PMID: 28947855.

(Three patients on long term oxycodone who had significant liver dysfunction had symptoms of withdrawal probably due to increase in systemic levels of naloxone, but liver tests did not worsen).

Lau F, Gardiner M. Oxycodone/naloxone: An unusual adverse drug reaction. Aust Fam Physician. 2017;46:42–3. PubMed PMID: 28189131.

(52 year old woman with chronic liver disease was switched from regular oxycodone to a fixed combination of oxycodone and naloxone and rapid developed withdrawal symptoms suspected to be due to the loss of first-pass clearance of naloxone by the liver dysfunction).

Cantrell FL, Sherrard J, Andrade M, Schaber B, McIntyre IM. A pediatric fatality due to accidental hydromorphone ingestion. Clin Toxicol (Phila). 2017;55:60–2. PubMed PMID: 27775447.

(3 year old boy was found to be dead and autopsy revealed no abnormalities except for presence of hydromorphone in blood and liver, his mother having a prescription for the drug found that several pills were missing).

Paul ABM, Simms L, Mahesan AM. Intentional heroin administration resulting in homicide in a 10-month old infant. Forensic Sci Int. 2018;290:e15–e18. PubMed PMID: 30017664.

(10 month of girl was found dead at home and autopsy revealed high levels of morphine in blood and liver as well as a single needle puncture mark in the left antecubital fossa; liver histopathology was referred to as unremarkable).

Opioids for pain. Med Lett Drugs Ther. 2018;60(1544):57–64. PubMed PMID: 29664446.

(Concise review of the mechanism of action, efficacy, safety and costs of opioids used for pain relief, discusses adverse events or short and long term use, but makes no mention of ALT elevations or hepatotoxicity).

Concheiro M, Chesser R, Pardi J, Cooper G. Postmortem toxicology of new synthetic opioids. Front Pharmacol. 2018;9:1210. PubMed PMID: 30416445.

(Summary of the chemical structures, pharmacology, relative potency and toxicology of the major synthetic opioids implicated in the ongoing opioid overdose epidemic; no discussion of hepatic injury).

Pattullo V, Pattullo GG, Strasser SI. Adverse effects of modified release oxycodone/naloxone in patients with moderate to severe liver impairment. Med J Aust. 2018;209:279–80. PubMed PMID: 30208822.

(Letter stressing the complications of oxycodone/naloxone therapy in patients with moderate or severe liver impairment marked by a decrease in analgesic effect and risk of withdrawal symptoms due to systemic absorption and lack of hepatic clearance of naloxone, a potent opiate antagonist).

Kinnunen M, Piirainen P, Kokki H, Lammi P, Kokki M. Updated clinical pharmacokinetics and pharmacodynamics of oxycodone. Clin Pharmacokinet. 2019;58:705–25. PubMed PMID: 30652261.

(Oxycodone is a full opioid agonist relatively selective for the μ receptor which is actively transported across the blood-brain barrier and is extensively metabolized by the liver via CYP3A4 [45%] and CYP 2D6 [29%], and plasma levels can be increased by CYP 3A4 inhibitors and renal dysfunction and to a lesser degree by CYP 2D6 inhibitors and hepatic dysfunction).