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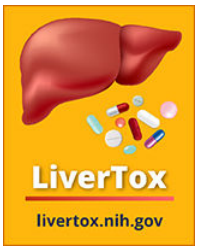

Alzheimer Disease Agents

Updated: February 3, 2020.

OVERVIEW

Alzheimer disease is a progressive degenerative brain condition that is the most common cause of dementia worldwide. Alzheimer disease affects at least 5 million persons in the United States, including approximately 1% of individuals in their 60's and up to 8% of those above the age of 85 years. The usual presentation is insidious with impaired memory and cognition and change in personality. The course is generally progressive with eventual mental and physical disability and death due to complications of immobility. The cause of Alzheimer disease is not known, but it is characterized by marked atrophy of the cerebral cortex and loss of neurons. Histologically, Alzheimer disease is marked by senile plaques, spherical accumulations of β-amyloid, degenerating neuronal processes and neurofibrillary tangles. Functionally, there appears to be impairment of cholinergic transmission. The increasing prevalence of Alzheimer disease in the elderly population has led to an increasing appreciation of the importance and the medical and social burden of Alzheimer disease. Early detection has led to attempts at therapy, the major goal being amelioration or slowing of its progressive course. Several medications have been found to alleviate some of the symptoms and signs of Alzheimer disease, but none have been proven to affect its ultimate course and outcome.

The pharmacotherapy of Alzheimer disease has focused on increasing cholinergic function in the brain. Acetylcholine precursors, such as choline and lecithin, have not proven beneficial, but inhibition of acetylcholine metabolism using inhibitors of acetylcholinesterase has been found to be partially successful in improving symptoms of Alzheimer disease. Four acetylcholinesterase inhibitors have been approved for use for Alzheimer disease in the United States: tacrine (Cognex: 1993), donepezil (Aricept: 1996), galantamine (Razadyne: 2001), and rivastigmine (Exelon: 2002). An alternative approach to treatment of Alzheimer disease is inhibition of N-methyl-D-aspartate (NMDA) glutamate receptors which is thought to lead to less excitotoxic injury to the brain. A single NMDA receptor inhibitor has been approved for use in Alzheimer disease in the United States: memantine (Namenda: 2003).

Therapy with tacrine has been associated with a very high rate of serum enzyme elevations, which can be dramatic although usually not associated with symptoms, jaundice or clinically apparent liver injury. Nevertheless, because of this side effect and the availability of other better tolerated cholinesterase inhibitors, tacrine is now no longer used. Except for tacrine, the drugs used for Alzheimer disease are rare causes of acute liver injury and have a low rate of associated serum enzyme elevations. The references on hepatotoxicity of the drugs used are listed together immediately after this introductory section. The agents referenced and discussed here include:

- Aducanumab
- Donepezil
- Galantamine

- Lecanemab
- Memantine
- Rivastigmine
- Tacrine

Increasing efforts in Alzheimer disease research have sought to identify means of preventing or slowing the progression of disease. Most attention has been focused on preventing or decreasing brain accumulation of amyloid-β oligomers and soluble aggregates that are believed to be the cause of neuronal damage in Alzheimer disease. However, clinical trials of monoclonal antibodies to amyloid-β (bapineuzumab, solanezumab) and small molecule inhibitors of β-secretase, the rate-limiting enzyme of amyloid-β production (verubecestat, atabecestat, lanabecestat, elenbecestat) have failed to show benefit in early or late Alzheimer disease. Indeed, some of these agents were associated with worsening of symptoms and signs of Alzheimer disease, others were withdrawn for further evaluation because of suspected hepatotoxicity (atabecestat). These agents are not in current use and are not discussed individually in LiverTox. Selected references on these agents are given in the Annotated Bibliography below.

ANNOTATED BIBLIOGRAPHY

References updated: 03 February 2020

Zimmerman HJ. 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. 709-42.

(Expert review of hepatotoxicity published in 1999; tacrine, the first cholinesterase inhibitor approved for use in Alzheimer disease, was associated with a very high rate of serum ALT elevations [~50%], but rarely caused clinically apparent liver injury; the other Alzheimer disease agents are not discussed).

Larrey D, Ripault MP. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 518.

(Review of hepatotoxicity of psychotropic agents; drugs for Alzheimer disease are not specifically discussed).

Roberson ED. Alzheimer's disease. Treatment of central nervous system degenerative disorders. 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. 333-5.

(Textbook of pharmacology and therapeutics).

Chatellier G, Lacomblez L. Tacrine (tetrahydroaminoacridine; THA) and lecithin in senile dementia of the Alzheimer type: a multicentre trial. Groupe Françs d'Etude de la Tetrahydroaminoacridine. BMJ. 1990;300:495–9. PubMed PMID: 2107926.

(In a randomized controlled crossover trial of tacrine in 67 patients with Alzheimer disease, 9 patients [13%] developed significant ALT or AST elevations, usually arising after 2-8 weeks of therapy, ALT 85-2115 U/L, one patient developed jaundice which resolved within 3-4 weeks of stopping).

Ames DJ, Bhathal PS, Davies BM, Fraser JR, Gibson PR, Roberts S. Heterogeneity of adverse hepatic reactions to tetrahydroaminoacridine. Aust N Z J Med. 1990;20:193–5. PubMed PMID: 2344330.

(5 of 14 patients [36%] taking tacrine for Alzheimer disease developed abnormal liver tests [ALT 106-422 U/L, GTT 20-71 U/L, bilirubin normal], one was symptomatic; liver biopsies showed focal necrosis, fat and one patient with granulomas, all resolved with stopping the drug or lowering the dose).

Hammel P, Larrey D, Bernuau J, Kalafat M, Fréaux E, Babany G, Degott C, et al. Acute hepatitis after tetrahydroaminoacridine administration for Alzheimer's disease. J Clin Gastroenterol. 1990;12:329–31. PubMed PMID: 2362104.

(A 76 year old woman with Alzheimer disease developed fever and jaundice 20 days after starting tacrine [bilirubin 5.0 mg/dL, ALT ~1800 U/L, Alk P 125 U/L, prothrombin index 40%], with rapid resolution on stopping, all liver tests falling to normal within 6 weeks).

O'Brien JT, Eagger S, Levy R. Effects of tetrahydroaminoacridine on liver function in patients with Alzheimer's disease. Age Ageing. 1991;20:129–31. PubMed PMID: 2053502.

(Prospective analysis of liver tests in 30 patients with Alzheimer disease treated with tacrine; 50% developed AST elevations within 17-38 days, 8 had clinical symptoms but none had jaundice, all resolved within 3-23 days after stopping or dose reduction; 6 were restarted and 5 tolerated therapy long term).

Farlow M, Gracon SI, Hershey LA, Lewis KW, Sadowsky CH, Dolan-Ureno J. A controlled trial of tacrine in Alzheimer's disease. The Tacrine Study Group. JAMA. 1992;268:2523–9. PubMed PMID: 1404819.

(Among 468 patients with Alzheimer disease treated with tacrine or placebo, ALT elevations [>3 times ULN] occurred in 25% of tacrine treated, but in none of placebo treated patients; all elevations were reversible and asymptomatic, usually arising in the first 8 weeks of treatment and resolving within 7-71 days of stopping).

Knapp MJ, Knopman DS, Solomon PR, Pendlebury WW, Davis CS, Gracon SI. A 30-week randomized controlled trial of high-dose tacrine in patients with Alzheimer's disease. The Tacrine Study Group. JAMA. 1994;271:985–91. PubMed PMID: 8139083.

(In a randomized controlled trial of tacrine vs placebo in 653 patients with Alzheimer disease, some degree of ALT elevation occurred in 54% and elevations >3 times ULN in 28% of tacrine-treated patients, but no patient had jaundice and most were asymptomatic, all resolved on stopping tacrine).

Watkins PB, Zimmerman HJ, Knapp MJ, Gracon SI, Lewis KW. Hepatotoxic effects of tacrine administration in patients with Alzheimer's disease. JAMA. 1994;271:992–8. PubMed PMID: 8139084.

(In depth analysis of liver test abnormalities occurring in 2446 patients on tacrine in multi-center trials; ALT elevations occurred in 49%, were >3 times ULN in 25%, >10 times ULN 6%, and >20 times ULN in 2%; usually arising within 6-8 weeks of starting, with no symptoms or minimal nausea and fatigue even when ALT >10 times ULN, eosinophilia in 23-44% but no rash, more rapid but less severe recurrence on rechallenge, nevertheless 88% could continue tacrine; more common in women than men).

Fulton B, Benfield P. Galanthamine. Drugs Aging. 1996;9:60–5. PubMed PMID: 8818586.

(Review of pharmacology, efficacy and safety of galantamine in Alzheimer disease; most side effects were due to its cholinergic properties, including nausea, vomiting, abdominal pain, diarrhea, anxiety and dizziness; "to date, elevations in liver enzymes or other signs of liver toxicity have not been reported with galanthamine").

Gracon SI, Knapp MJ, Berghoff WG, Pierce M, DeJong R, Lobbestael SJ, Symons J, et al. Safety of tacrine: clinical trials, treatment IND, and postmarketing experience. Alzheimer Dis Assoc Disord. 1998;12:93–101. PubMed PMID: 9651138.

(Review of safety including hepatotoxicity of tacrine based upon registration trials and postmarketing adverse event reporting; ALT levels rise to >3 times the ULN in at least 25% of patients, but are usually asymptomatic and not associated with jaundice).

Rösler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal-Bianco P, Stälin HB, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. BMJ. 1999;318:633–8. PubMed PMID: 10066203.

(Controlled trial of two doses of rivastigmine vs placebo for 26 weeks in 725 patients with Alzheimer disease, no differences in ALT elevations between treatment and placebo arms; side effects included nausea, dizziness, headache, anorexia, fatigue and abdominal pain).

Wilcock GK, Lilienfeld S, Gaens E. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomized controlled trial. Galantamine International-1 Study Group. BMJ. 2000;321:1445–9. PubMed PMID: 11110737.

(Controlled trial of 6 months of two doses of galantamine vs placebo in 653 patients with Alzheimer disease: side effects included nausea, diarrhea, headache, anorexia and weight loss, but there were "no consistent trends or clinically important differences" in blood chemistry results).

Barbare JC, Imbert A, Benkirane A. Presse Med. 2001;30:673–6. [Recent developments concerning drug-induced liver toxicity]. French. PubMed PMID: 11360729.

(Review of importance of central reporting of drug induced liver injury, providing examples of recently described hepatotoxic reactions, including 3 recent cases of hepatocellular injury due to riluzole).

Verrico MM, Nace DA, Towers AL. Fulminant chemical hepatitis probably associated with donepezil and sertraline therapy. J Amer Geriat Soc. 2000;48:1659–63. PubMed PMID: 11129758.

(83 year old woman developed jaundice 10 days after starting donepezil and 5 months after starting sertraline [bilirubin 5.6 rising to 22.6 mg/dL, ALT 529 U/L, Alk P 369 U/L, peak INR 1.8], resolving after stopping both in the next 4 months).

Reisberg B, Doody R, Stöer A, Schmitt F, Ferris S, Mös HJ; Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med. 2003;348:1333–41. PubMed PMID: 12672860.

(Controlled trial of 28 weeks of memantine vs placebo in 252 patients with Alzheimer disease: no differences in rates of any adverse event; serum ALT levels and hepatotoxicity not mentioned).

Pirttilä T, Wilcock G, Truyen L, Damaraju CV. Long-term efficacy and safety of galantamine in patients with mild-to-moderate Alzheimer's disease: multicenter trial. Eur J Neurol. 2004;11:734–41. PubMed PMID: 15525294.

(Results of continuing galantamine for 24 months in 491 patients with Alzheimer disease; reported no instances of liver toxicity and "no clinically relevant trends" in "clinical laboratory parameters").

Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I; Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA. 2004;291:317–24. PubMed PMID: 14734594.

(Controlled trial of 24 weeks of memantine vs placebo in 404 patients with Alzheimer disease receiving donepezil: side effects that were more common with memantine were confusion and headache; "No clinically significant differences were detected between treatment groups...in laboratory tests").

Seltzer B, Zolnouni P, Nunez M, Goldman R, Kumar D, Ieni J, Richardson S. Donepezil "402" Study Group. Efficacy of donepezil in early-stage Alzheimer disease: a randomized placebo-controlled trial. Arch Neurol. 2004;61:1852–6. PubMed PMID: 15596605.

(Controlled trial of 24 weeks of donepezil vs placebo in 153 patients with early Alzheimer disease: side effects included diarrhea, nausea, fatigue, dizziness and insomnia; no mention of ALT elevations or hepatotoxicity).

Winblad B, Wimo A, Engedal K, Soininen H, Verhey F, Waldemar G, Wetterholm AL, et al. 3-year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy. Dement Geriatr Cogn Disord. 2006;21:353–63. PubMed PMID: 16508298.

(Continuation of donepezil for 3 years in 81 patients with Alzheimer disease reported no clinically significant changes in laboratory test results).

Winblad B, Kilander L, Eriksson S, Minthon L, Båman S, Wetterholm AL, Jansson-Blixt C, et al; Severe Alzheimer's Disease Study Group. Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. Lancet. 2006;367:1057–65. PubMed PMID: 16581404.

(Controlled trial of 6 months of donepezil vs placebo in 248 patients with severe Alzheimer disease; side effects were mostly mild and did not differ between donepezil and placebo treated patients; there were "no great changes in the results of laboratory tests").

Bullock R. Efficacy and safety of memantine in moderate-to-severe Alzheimer disease: the evidence to date. Alzheimer Dis Assoc Disord. 2006;20:23–9. PubMed PMID: 16493232.

(Review of the safety of memantine from 3 pivotal controlled trials and more than 100,000 patient-years of use: overall rates of side effects were not different from placebo, were mild-to-moderate, and often considered unrelated; no mention of hepatotoxicity).

Seltzer B. Donepezil: an update. Expert Opin Pharmacother. 2007;8:1011–23. PubMed PMID: 17472546.

(Review of safety and efficacy of donepezil, the most commonly used agent in therapy of Alzheimer disease; no discussion of ALT elevations or hepatotoxicity).

Farlow MR, Cummings JL. Effective pharmacologic management of Alzheimer's disease. Am J Med. 2007;120:388–97. PubMed PMID: 17466645.

(Review of safety and efficacy of medications for Alzheimer disease; no discussion of hepatotoxicity).

Bakchine S, Loft H. Memantine treatment in patients with mild to moderate Alzheimer's disease: results of a randomised, double-blind, placebo-controlled 6-month study. J Alzheimers Dis. 2008;13:97–107. PubMed PMID: 18334761.

(Controlled trial of 24 weeks of memantine vs placebo in 470 patients with Alzheimer disease: adverse events occurred in similar rates with memantine and placebo, were all mild-to-moderate, and there "were no clinically meaningful differences between treatment groups" in laboratory tests).

Ferrara N, Corbi G, Capuano A, Filippelli A, Rossi F. Memantine-induced hepatitis with cholestasis in a very elderly patient. Ann Intern Med. 2008;148:631–2. PubMed PMID: 18413635.

(92 year old woman developed jaundice and pruritus 16 days after starting memantine for dementia [bilirubin 4.3 mg/dL, ALT 132 U/L, Alk P 912 U/L], resolving within 3 weeks of stopping).

Dierckx RIR, Vandewoude MFJ. Donepezil-related toxic hepatitis. Acta Clin Belg. 2008;63:339–42. PubMed PMID: 19186568.

(90 year old man with Alzheimer disease developed abdominal pain and jaundice 2 weeks after starting donepezil [bilirubin 5.9 rising to 22.6 mg/dL, ALT 329 U/L, Alk P 944 U/L], resolving over the next 3 months).

Hansen RA, Gartlehner G, Webb AP, Morgan LC, Moore CG, Jonas DE. Efficacy and safety of donepezil, galantamine, and rivastigmine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. Clin Interv Aging. 2008;3:211–25. PubMed PMID: 18686744.

(Systematic review of 3 cholinesterase inhibitors in Alzheimer disease; most common adverse events were nausea [19%], vomiting [13%], diarrhea [11%] and weight loss [9%] and withdrawal for adverse events in 11-21%; no mention of ALT elevations or hepatotoxicity).

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 in the US collected between 2004 and 2008; none were attributed to a drug used to treat Alzheimer disease).

Mumoli N, Carmignani G, Luschi R, Cei M, Chiavistelli P. Hepatitis with cholestasis caused by rivastigmine transdermal patch. Am J Gastroenterol. 2009;104:2859–60.

(84 year old woman developed jaundice and rash 2 months after starting transdermal rivastigmine for Alzheimer disease [bilirubin 3.0 mg/dL, ALT 857 U/L, Alk P 344 U/L, eosinophils 8%], resolving within 5 weeks of stopping).

Mayeux R. Early Alzheimer's disease. N Engl J Med. 2010;362:2194–201. PubMed PMID: 20558370.

(Case discussion and review of current understanding of Alzheimer disease including role of therapy; common side effects of cholinesterase inhibitors include nausea, vomiting, anorexia, diarrhea, dizziness, muscle cramps, insomnia and vivid dreams; memantine can cause constipation, dizziness, headache and body pains; no mention of hepatotoxicity).

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 were attributed to drugs used to treat Alzheimer disease).

Farlow M, Veloso F, Moline M, Yardley J, Brand-Schieber E, Bibbiani F, Zou H, et al. Safety and tolerability of donepezil 23 mg in moderate to severe Alzheimer's disease. BMC Neurol. 2011;11:57. PubMed PMID: 21612646.

(Among 1434 patients with Alzheimer disease treated with 10 vs 23 mg of donepezil daily for 24 weeks, cholinergic side effects were more common with the higher dose, but there were no differences in frequency of "clinically important" abnormal laboratory values).

Dubois B, Tolosa E, Katzenschlager R, Emre M, Lees AJ, Schumann G, Pourcher E, et al. Donepezil in Parkinson's disease dementia: a randomized, double-blind efficacy and safety study. Mov Disord. 2012;27:1230–8. PubMed PMID: 22915447.

(Among 550 patients with Alzheimer disease treated with two doses of donepezil or placebo for 24 weeks, nausea, tremor, diarrhea, insomnia and anorexia were more frequent in patients on donepezil, but "Laboratory tests and physical examination data remained largely unchanged").

Tariot P, Salloway S, Yardley J, Mackell J, Moline M. Long-term safety and tolerability of donepezil 23 mg in patients with moderate to severe Alzheimer's disease. BMC Res Notes. 2012;5:283. PubMed PMID: 22681723.

(Among 915 patients with Alzheimer disease treated with donepezil in a dose of 23 vs 10 mg daily, cholinergic side effects were more common at the higher dose, but "there were no changes in laboratory test values").

Tan CC, Yu JT, Wang HF, Tan MS, Meng XF, Wang C, Jiang T, et al. Efficacy and Safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis. 2014;41:615–31. PubMed PMID: 24662102.

(Systematic review of safety and efficacy of 4 Alzheimer drugs does not mention ALT elevations or hepatotoxicity).

Tricco AC, Soobiah C, Berliner S, Ho JM, Ng CH, Ashoor HM, Chen MH, Hemmelgarn B, Straus SE. Efficacy and safety of cognitive enhancers for patients with mild cognitive impairment: a systematic review and meta-analysis. CMAJ. 2013 Nov 5;185(16):1393–401. PubMed PMID: 24043661.

(Systematic review of 8 clinical trials and 3 reports on the safety and efficacy of Alzheimer drugs mentions that side effects of nausea, diarrhea, vomiting and headaches were usually more frequent with the active drugs compared to placebo; no mention of ALT elevations or clinically apparent liver injury).

Ikeda M, Mori E, Kosaka K, Iseki E, Hashimoto M, Matsukawa N, Matsuo K, Nakagawa M; Donepezil-DLB Study Investigators. Long-term safety and efficacy of donepezil in patients with dementia with Lewy bodies:

results from a 52-week, open-label, multicenter extension study. Dement Geriatr Cogn Disord. 2013;36(3-4):229–41. PubMed PMID: 23949147.

(Among 108 patients with dementia treated with donepezil for up to 52 weeks, no patient developed clinically apparent liver injury; 12 patients developed CPK elevations, but ALT elevations were not mentioned).

Salloway S, Mintzer J, Cummings JL, Geldmacher D, Sun Y, Yardley J, Mackell J. Subgroup analysis of US and non-US patients in a global study of high-dose donepezil (23 mg) in moderate and severe Alzheimer's disease. Am J Alzheimers Dis Other Demen. 2012;27:421–32. PubMed PMID: 22930699.

(Reanalysis of safety and efficacy of a multinational trial of donepezil in Alzheimer disease found that rates of nausea, vomiting, anorexia, weight loss, fatigue and incontinence where twice as high in patients receiving higher doses of donepezil; no mention of ALT elevations or hepatotoxicity).

Gauthier S, Robillard A, Cohen S, Black S, Sampalis J, Colizza D, de Takacsy F, et al; EMBRACE investigators. Real-life effectiveness and tolerability of the rivastigmine transdermal patch in patients with mild-to-moderate Alzheimer's disease: the EMBRACE study. Curr Med Res Opin. 2013;29:989–1000. PubMed PMID: 23647369.

(Among 969 Canadian patients with Alzheimer disease treated with rivastigmine patch for 18 months, 18% stopped treatment because of adverse events, usually skin reactions or nausea/vomiting; no mention of ALT elevations or clinically apparent liver injury).

Mäurer M, Ortler S, Baier M, Meergans M, Scherer P, Hofmann W, Tracik F. Randomised multicentre trial on safety and efficacy of rivastigmine in cognitively impaired multiple sclerosis patients. Mult Scler. 2013;19:631–8. PubMed PMID: 23069874.

(Among 86 patients with multiple sclerosis and cognitive decline treated with rivastigmine or placebo patches for 16 weeks, side effects were similar in the two groups; no mention of ALT elevations or hepatotoxicity).

Ikeda M, Mori E, Kosaka K, Iseki E, Hashimoto M, Matsukawa N, Matsuo K, Nakagawa M; Donepezil-DLB Study Investigators. Long-term safety and efficacy of donepezil in patients with dementia with Lewy bodies: results from a 52-week, open-label, multicenter extension study. Dement Geriatr Cogn Disord. 2013;36:229–41. PubMed PMID: 23949147.

(Among 108 patients with dementia treated with open label donepezil for 52 weeks, there were no hepatic serious adverse events; no mention of ALT levels).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology. 2013;144:1419–25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, but none of the cases were attributed to a drug used to treat Alzheimer disease).

Hager K, Baseman AS, Nye JS, Brashear HR, Han J, Sano M, Davis B, Richards HM. Effects of galantamine in a 2-year, randomized, placebo-controlled study in Alzheimer's disease. Neuropsychiatr Dis Treat. 2014;10:391–401. PubMed PMID: 24591834.

(Among 2045 patients with Alzheimer disease treated with galantamine or placebo for up to 2 years, symptoms of nausea, vomiting, and fatigue were slightly more frequent with galantamine than placebo, but serious adverse events were similar in the two groups and "No clinically meaningful changes were observed in... laboratory tests").

Nakamura Y, Kitamura S, Homma A, Shiosakai K, Matsui D. Efficacy and safety of memantine in patients with moderate-to-severe Alzheimer's disease: results of a pooled analysis of two randomized, double-blind, placebo-controlled trials in Japan. Expert Opin Pharmacother. 2014;15:913–25. PubMed PMID: 24673497.

(Among 633 Japanese patients with Alzheimer disease treated with either memantine or placebo, the rate of adverse events was similar in the two groups; no mention of ALT elevations or clinically apparent liver injury).

Dysken MW, Sano M, Asthana S, Vertrees JE, Pallaki M, Llorente M, Love S, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial. JAMA. 2014;311:33–44. PubMed PMID: 24381967.

(Among 561 patients with Alzheimer disease treated with vitamin E, memantine, the combination or placebo for an average of 2.3 years, overall adverse events were similar in the 4 groups, but serious infections were more common with memantine than placebo (15% vs 7%); no mention of ALT elevations or hepatotoxicity).

Emre M, Poewe W, De Deyn PP, Barone P, Kulisevsky J, Pourcher E, van Laar T, et al. Long-term safety of rivastigmine in parkinson disease dementia: an open-label, randomized study. Clin Neuropharmacol. 2014;37(1):9–16. PubMed PMID: 24434526.

(Among 583 patients with Parkinson disease dementia treated with either rivastigmine capsules or patch, adverse events were more frequent with capsules, particularly tremor, nausea, vomiting, diarrhea and syncope; no mention of ALT elevations or hepatotoxicity).

Chew AP, Lim WS, Tan KT. Donepezil-induced hepatotoxicity in an elderly adult taking fluoxetine. J Am Geriatr Soc. 2014;62:2009–11. PubMed PMID: 25333550.

(A 79 year old man with depression, Alzheimer disease and cirrhosis due to hepatitis was taking high doses of fluoxetine [80 mg daily] and lamivudine and developed fatigue and anorexia with abnormal liver tests 6 weeks after starting donepezil [bilirubin 1.5 mg/dL, ALT 177 U/L, Alk P 127 U/L], which resolved within 8 weeks of stopping both and did not recur on restarting sertraline along with and memantine instead of donepezil).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A, Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America: an analysis of published reports. Ann Hepatol. 2014;13:231–9. PubMed PMID: 24552865.

(Among 176 reports of drug induced liver injury from Latin America published between 1996 and 2012, none were attributed to a drug for Alzheimer disease).

Salloway S, Sperling R, Fox NC, Blennow K, Klunk W, Raskind M, Sabbagh M, et al; Bapineuzumab 301 and 302 Clinical Trial Investigators. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. N Engl J Med. 2014;370:322–33. PubMed PMID: 24450891.

(Among 2452 adults with mild-to-moderate Alzheimer disease treated in two controlled trials with bapineuzumab or placebo for 1.5 years, there was no improvement in symptoms of dementia, but amyloid-related imaging abnormalities arose in 4% to 15% of bapineuzumab treated subjects compared to 0.2% of placebo recipients).

Doody RS, Thomas RG, Farlow M, Iwatsubo T, Vellas B, Joffe S, Kieburtz K, et al; Alzheimer's Disease Cooperative Study Steering Committee. Solanezumab Study Group. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. N Engl J Med. 2014;370:311–21. PubMed PMID: 24450890.

(Among 2052 patients with mild-to-moderate Alzheimer disease treated in 2 trials with solanezumab or placebo for 18 months, there were no improvements in clinical symptoms with therapy compared to placebo and no differences in adverse event rates; no mention of 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 due to a drug for Alzheimer disease).

Kröger E, Mouls M, Wilchesky M, Berkers M, Carmichael PH, van Marum R, Souverein P, et al. Adverse drug reactions reported with cholinesterase inhibitors: an analysis of 16 years of individual case safety reports from VigiBase. Ann Pharmacother. 2015;49:1197–206. PubMed PMID: 26324356.

(Analysis of spontaneous adverse event reports made between 2006 and 2013 to a WHO drug monitoring database identified 16,995 serious adverse events in patients receiving cholinesterase inhibitors, 121 of which were hepatobiliary, including 47 for donepezil, 53 rivastigmine and 21 galantamine; no details provided).

Ikeda M, Mori E, Matsuo K, Nakagawa M, Kosaka K. Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled, confirmatory phase III trial. Alzheimers Res Ther. 2015;7:4. PubMed PMID: 25713599.

(Among 142 patients with dementia with Lewy bodies treated with donepezil [5 or 10 mg] vs placebo for 12 weeks, adverse events were mild-to-moderate and those more frequent with donepezil were anorexia, nausea and Parkinson disease symptoms; no mention of ALT elevations or hepatotoxicity).

Wang HF, Yu JT, Tang SW, Jiang T, Tan CC, Meng XF, Wang C, et al. Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis. J Neurol Neurosurg Psychiatry. 2015;86:135–43. PubMed PMID: 24828899.

(Systematic review of 10 trials of Alzheimer disease drugs in Parkinson disease and other forms of dementia reported that the common adverse events were cholinergic in nature [anorexia, nausea, diarrhea] and were generally mild-to-moderate in severity; serious adverse events were similar to rates with placebo; no mention of ALT elevations or hepatotoxicity).

Mohammad D, Chan P, Bradley J, Lanctôt K, Herrmann N. Acetylcholinesterase inhibitors for treating dementia symptoms - a safety evaluation. Expert Opin Drug Saf. 2017;16:1009–19. PubMed PMID: 28678552.

(Review of safety of donepezil, galantamine and rivastigmine in Alzheimer disease concludes that adverse events are "generally mild", mostly gastrointestinal, comparable among the different agents, but usually greater with higher doses and less with transdermal formulations).

Keskin AD, Kekuš M, Adelsberger H, Neumann U, Shimshek DR, Song B, Zott B, et al. BACE inhibition-dependent repair of Alzheimer's pathophysiology. Proc Natl Acad Sci U S A. 2017;114:8631–6. PubMed PMID: 28739891.

(In a mouse model of Alzheimer disease, reduction in β-secretase activity decreased cerebral amyloid β proteins in the brain and improved measures of neuronal function).

Egan MF, Kost J, Tariot PN, Aisen PS, Cummings JL, Vellas B, Sur C, et al. Randomized trial of verubecestat for mild-to-moderate Alzheimer's disease. N Engl J Med. 2018;378:1691–703. PubMed PMID: 29719179.

(Among 1958 patients with Alzheimer disease treated with verubecestat [12 or 40 mg] versus placebo daily for 18 months, symptoms of dementia did not improve, and adverse events were more frequent with active drug; there were no liver related severe adverse events).

Panza F, Lozupone M, Solfrizzi V, Sardone R, Piccininni C, Dibello V, Stallone R, et al. BACE inhibitors in clinical development for the treatment of Alzheimer's disease. Expert Rev Neurother. 2018;18:847–57. PubMed PMID: 30277096.

(Review of the mechanism of action and results of clinical trials of β-site amyloid precursor protein cleaving enzyme [BACE] inhibitors [veru-, ata-, lana-, and elenbecestat] as therapy of Alzheimer disease mentions that most failed to show efficacy in human trials and that trials of atabecestat were discontinued because of serious serum enzyme elevations in some patients).

Timmers M, Streffer JR, Russu A, Tominaga Y, Shimizu H, Shiraishi A, Tatikola K, et al. Pharmacodynamics of atabecestat (JNJ-54861911), an oral BACE1 inhibitor in patients with early Alzheimer's disease: randomized, double-blind, placebo-controlled study. Alzheimers Res Ther. 2018;10:85. PubMed PMID: 30134967.

(Among 33 patients with early Alzheimer disease treated with atabecestat [10 or 50 mg] or placebo once daily for 4 weeks, there were no changes in cognition and no "clinically significant trends in changes from baseline in …liver function tests").

Yip LY, Aw CC, Lee SH, Hong YS, Ku HC, Xu WH, Chan JMX, et al. The liver-gut microbiota axis modulates hepatotoxicity of tacrine in the rat. Hepatology. 2018;67:282–95. PubMed PMID: 28646502.

(In Lister hooded rats, tacrine administration resulted in variable increases in ALT and AST with higher levels correlating with higher systemic exposure, which could be modified by changing the intestinal bacterial flora [microbiome], which was likely the result of bacterial deglucuronidation of tacrine during enterohepatic recycling).

Dou KX, Tan MS, Tan CC, Cao XP, Hou XH, Guo QH, Tan L, et al. Comparative safety and effectiveness of cholinesterase inhibitors and memantine for Alzheimer's disease: a network meta-analysis of 41 randomized controlled trials. Alzheimers Res Ther. 2018;10:126. PubMed PMID: 30591071.

(Meta-analysis of 41 published randomized controlled trials of drugs for Alzheimer disease concluded that all had beneficial effects on cognition and function but not on neuropsychiatric symptoms, and all had adverse effects but memantine showed "the best profile of acceptability"; no mention of ALT elevations or hepatotoxicity).

Khoury R, Rajamanickam J, Grossberg GT. An update on the safety of current therapies for Alzheimer's disease: focus on rivastigmine. Ther Adv Drug Saf. 2018;9:171–8. PubMed PMID: 29492246.

(Review of the safety of Alzheimer disease agents discusses gastrointestinal adverse events, cardiac side effects, skin reactions [to transdermal formulations] and neuropsychiatric effects, but not hepatic adverse events).

Arai H, Hashimoto N, Sumitomo K, Takase T, Ishii M. Disease state changes and safety of long-term donepezil hydrochloride administration in patients with Alzheimer's disease: Japan-Great Outcome of Long-term trial with Donepezil (J-GOLD). Psychogeriatrics. 2018;18:402–11. PubMed PMID: 29993162.

(Among more than 10,000 Japanese patients with Alzheimer disease treated with donepezil for 48 months, adverse events included anorexia, nausea, diarrhea, agitation, anger, dizziness, delusions, insomnia and restlessness, but there were no major safety problems; hepatic adverse events were not mentioned).

Matsunaga S, Kishi T, Nomura I, Sakuma K, Okuya M, Ikuta T, Iwata N. The efficacy and safety of memantine for the treatment of Alzheimer's disease. Expert Opin Drug Saf. 2018;17:1053–61. PubMed PMID: 30222469.

(Review of the literature on efficacy and safety of memantine concluded that it improves cognitive function and behavioral disturbances and is well tolerated, most common adverse events being somnolence and weight gain; does not discuss ALT elevations or hepatotoxicity, but mentions that hepatitis is listed as an adverse event in the product label).

Bhattacharjee S, Patanwala AE, Lo-Ciganic WH, Malone DC, Lee JK, Knapp SM, Warholak T, Burke WJ. Alzheimer's disease medication and risk of all-cause mortality and all-cause hospitalization: A retrospective cohort study. Alzheimers Dement (N Y). 2019;5:294–302. PubMed PMID: 31338414.

(Among more than 20,000 Medicare beneficiaries receiving Alzheimer disease drugs, overall survival was better for those on donepezil than memantine or rivastigmine; no mention of serious hepatic adverse events or liver related deaths).

Hong YJ, Han HJ, Youn YC, Park KW, Yang DW, Kim S, Kim HJ, et al. ODESA study (Optimal Dose Escalation Strategy to Successful Achievement of High Dose Donepezil 23 mg). Safety and tolerability of donepezil 23 mg with or without intermediate dose titration in patients with Alzheimer's disease taking donepezil 10 mg:

a multicenter, randomized, open-label, parallel-design, three-arm, prospective trial. Alzheimers Res Ther. 2019;11:37. PubMed PMID: 31039806.

(Among 160 patients with Alzheimer disease receiving donepezil and undergoing dose escalation from 10 to 23 mg daily, there were few gastrointestinal side effects and lower rates of nausea and dizziness in those with an initial titration period to the higher dose; no mention of ALT elevations or hepatotoxicity).

Shumar J, Ordway S, Junga Z, Sadowski B, Torres D. Memantine-induced liver injury with probable causality as assessed using the Roussel Uclaf Causality Assessment Method (RUCAM). ACG Case Rep J. 2019;6:e00184. PubMed PMID: 31737715.

(An 86 year old man with Alzheimer disease was found to have abnormal liver tests without symptoms or jaundice, 2 months after adding memantine to his usual medications [ALT 439 U/L, Alk P 169 U/L, bilirubin 0.9 mg/dL], resolving within 6 months of stopping memantine only).

Chang CC, Peng GS, Lai TJ, Li CH, Liu CK. A 48-week, multicenter, open-label, observational study evaluating oral rivastigmine in patients with mild-to-moderate Alzheimer's disease in Taiwan. Adv Ther. 2019;36:1455–64. PubMed PMID: 30953330.

(Among 151 Taiwanese patients with Alzheimer disease treated with rivastigmine, common side effects were dizziness [13%] and nausea [9%], and there were "no new or unexpected" adverse events and no mention of ALT elevations or hepatotoxicity).

Carney G, Bassett K, Wright JM, Maclure M, McGuire N, Dormuth CR. Comparison of cholinesterase inhibitor safety in real-world practice. Alzheimers Dement (N Y). 2019;5:732–9. PubMed PMID: 31921965.

(Among 29,047 Canadian patients with Alzheimer disease who initiated anticholinesterase therapy between 2007 and 2016, all-cause mortality and serious cardiovascular event rates were lower in those receiving galantamine than those on donepezil; no mention of hepatic adverse events or liver related deaths).

Matsunaga S, Fujishiro H, Takechi H. Efficacy and safety of cholinesterase inhibitors for mild cognitive impairment: a systematic review and meta-analysis. J Alzheimers Dis. 2019;71:513–23. PubMed PMID: 31424411.

(Systematic review of 14 randomized controlled trials of anticholinesterase drugs in Alzheimer disease concluded that the agents had slight efficacy in ameliorating symptoms but a moderate rate of discontinuation because of adverse events such as abnormal dreams, dizziness, headache, insomnia, diarrhea, muscle cramps, nausea and weight loss; no mention of discontinuations because of ALT elevations or hepatotoxicity).

Li DD, Zhang YH, Zhang W, Zhao P. Meta-analysis of randomized controlled trials on the efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease. Front Neurosci. 2019;13:472. PubMed PMID: 31156366.

(Meta-analysis of 36 controlled trials of drugs for Alzheimer disease focusing upon relative efficacy and rates of discontinuation in comparison to placebo).

Wessels AM, Tariot PN, Zimmer JA, Selzler KJ, Bragg SM, Andersen SW, Landry J, et al. Efficacy and safety of lanabecestat for treatment of early and mild Alzheimer disease: The AMARANTH and DAYBREAK-ALZ Randomized Clinical Trials. JAMA Neurol. 2020;77(2):199–209. Erratum in: JAMA Neurol 2020; 77(9): 1179. PubMed PMID: 31764959.

(In a phase 3 trial of 2218 patients with early Alzheimer disease treated with lanabecestat [20 or 50 mg] or placebo daily, the study was discontinued early because of futility while adverse events included psychiatric symptoms, weight loss and hair color changes and "no change in pattern of potentially clinically significant…laboratory values… was observed").

Egan MF, Kost J, Voss T, Mukai Y, Aisen PS, Cummings JL, Tariot PN, et al. Randomized trial of verubecestat for prodromal Alzheimer's disease. N Engl J Med. 2019;380:1408–20. PubMed PMID: 30970186.

(Among 1454 patients with prodromal Alzheimer disease treated with verubecestat [12 or 40 mg] or placebo once daily for up to 48 months, cognitive function and daily functional status appeared to worsen with therapy while ALT elevations above 3 times ULN arose in 0.8% to 1.1% of verubecestat- vs 1.1% of placebo-recipients).

Egan MF, Mukai Y, Voss T, Kost J, Stone J, Furtek C, Mahoney E, et al. Further analyses of the safety of verubecestat in the phase 3 EPOCH trial of mild-to-moderate Alzheimer's disease. Alzheimers Res Ther. 2019;11:68. PubMed PMID: 31387606.

(Among 1454 patients with mild-to-moderate Alzheimer disease treated with verubecestat [12 or 40 mg] or placebo daily for up to 78 weeks, further analysis of safety showed no serious hepatic adverse events and ALT elevations were similar in frequency in all groups and ALT elevations with hyperbilirubinemia arising in 0.3% of verubecestat treated patients and 0.2% of placebo recipients).

Henley D, Raghavan N, Sperling R, Aisen P, Raman R, Romano G. Preliminary results of a trial of atabecestat in preclinical Alzheimer's disease. N Engl J Med. 2019;380:1483–5. PubMed PMID: 30970197.

(Among 557 patients with "preclinical" Alzheimer disease treated with atabecestat [5 or 25 mg] or placebo once daily for up to 18 months, hepatic related adverse events led to an early discontinuation of the trial, although the details were not provided).