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Anticonvulsants

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OVERVIEW

Anticonvulsant medications include many agents that have been incriminated in causing idiosyncratic drug induced liver disease. Indeed, several commonly used anticonvulsants (phenytoin, valproate, carbamazepine) are consistently ranked in the top causes of clinically apparent drug induced liver injury and are frequently listed in causes of drug induced acute liver failure. Because of the importance of pharmacotherapy of epilepsy, the potential hepatotoxicity of these agents has been considered acceptable. Nevertheless, attempts at developing safer agents of equivalent or superior efficacy continue.

Major anticonvulsants include hydantoin derivatives, barbiturates, benzodiazepines, succinimides, valproic acid, gamma amino butyric acid (GABA) precursors and analogues, inhibitors of DMDA receptors and a multitude of miscellaneous recently introduced agents. At least two dozen agents are licensed and approved for use as anticonvulsants in the United States. The anticonvulsants that are available in the United States, the likelihood score for hepatotoxicity, their year of introduction or approval and their major approved indications are shown in the Table which includes links to the individual agents with the full description and discussion of their potential for hepatiotoxicity.

Phenobarbital is the oldest antiepileptic medication still in use, having been introduced into clinical medicine in 1916. Phenobarbital is an aromatic anticonvulsant and, like phenytoin and carbamazepine, can cause the aromatic anticonvulsant hypersensitivity syndrome, a form of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Questions remain regarding the anticonvulsant efficacy of phenobarbital and it is now rarely used for this indication.

Phenytoin, formerly known as diphenylhydantoin, was introduced into use as an anticonvulsant in 1938 and remains one of the most commonly used medications for epilepsy. Fosphenytoin is an intravenous formulation of phenytoin that has been available since 1995 and is used for status epilepticus and as a substitute for oral phenytoin during surgery. Phenytoin is a well known cause of acute liver injury, which is usually part of the anticonvulsant hypersensitivity syndrome and can be severe and lead to acute liver failure and death.

Carbamazepine was introduced into use in 1963 for treatment of generalized seizures and with other carbamazepines (oxcarbazepine, eliscarbazepine) is still widely used. Carbamazepine can also cause the anticonvulsant hypersensitivity syndrome and is a well known cause of acute drug induced liver injury as well as serious cutaneous reactions such as Stevens Johnson syndrome and toxic epidermal necrolysis.

Lamotrigine is a more recently developed anticonvulsant that has broad antiseizure activity. Lamotrigine can also cause the anticonvulsant hypersensivity sydrome and has become one of the most common causes of clinically apparent drug-induced liver injury.

The benzodiazepines are both anxiolytic and antiepileptic and several including diazepam, clonazepam and clorazepate are used in the therapy of epilepsy. Benzodiazepines are also discussed under the antianxiolytic medications. They appear to act by enhancing gamma aminobutyric acid (GABA) receptor activity. While many benzodiazepines have antiseizure activity, only clonazepam and cloazepate are commonly used in long term treatment of epilepsy. Diazepam and other parentally administered benzodiazepams are also used for therapy of status epilepticus. Benzodiazepines have only rarely been implicated in causing drug induced liver injury and have not been implicated in the anticonvulsant hypersensitivity syndrome.

The succinimides are active against clonic motor seizures and absence seizures (petit mal) in humans. This class includes ethosuximide (1960) and methsuximide (1957).

Valproic acid or valproate is a branched chain carboxylic acid that was found to have antiseizure activity somewhat by accident. Valproate was introduced in 1978 and rapidly became a commonly used agent for partial seizures and for poorly controlled generalized seizures. Valproic acid is also used in the treatment of mood and bipolar disorders. Valproate can cause several distinctive forms of liver injury, ranging from asymptomatic serum aminotransferase elevations to an acute hepatitis which can be severe and even fatal, to a Reye syndrome like syndrome of hepatic dysfunction and microvesicular fatty liver. High doses of valproic acid can also cause stupor and coma from hyperammonemia without accompaning severe liver injury.

Topiramate is a sulfamate-substituted monosaccharide and unique and broadly active anticonvulsant introduced in 1996 that is still widely used. Topiramate is also used for prevention of migraine headaches, as a weight loss agent and (off label) for mood disorders and bipolar illness.

Levetiracetam is a pyrrolidine derivative and unique anticonvulsant introduced in 1999 that has been increasing used because of its safety and excellent tolerability. Levetiracetam binds to the synaptic vesicle glycoprotein SV2A and appears to act by inhibiting calcium channels which participate in neurotransmitter release. Levetiracetam has been linked to rare instances of drug induced liver disease, but not with the anticonvulsant hypersensivity syndrome. Brivaracetam is an anticonvulsant of similar structure and activity was approved in 2016.

Other agents active against seizures have been developed in recent years, many of which act by uncertain mechanisms and which belong to different classes of agents. These agents, their likelihood score, year of approval and major indications are given below.

ANTICONVULSANTS*			
Generic Name Brand Name	**Likelihood Score**	**Approval**	**Major Indications**
Brivaracetam Briviact	E	2016	Partial seizures
Cannabidiol Epidiolex	E*	2018	Seizures assocated with Lennox-Gastaut or Dravet syndrome
Carbamazepine Tegretol	A	1968	Partial, mixed and generalized seizures, trigeminal neuralgia
Clobazam Onfi	E	2011	Seizures assocated with Lennox-Gastaut syndrome
Clonazepam Klonopin	D	1975	Absence and myoclonic seizures, anxiety and panic disorders
Clorazepate Tranxene	E	1972	Partial seizures, anxiety disorders, and alcohol withdrawal

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Diazepam Valium	E	1963	Convulsions, anxiety disorders, muscle spasms
Eslicarbazepine Aptiom	D	2013	Partial seizures
Ethosuximide Zarontin	E	1960	Absence seizures
Ezogabine Potiga	E	2011	Partial seizures
Felbamate Febatol	B	1993	Refractory or severe epilepsy
Fosphenytoin Cerebyx	A	1996	Tonic-clonic seizures, status epilepticus
Gabapentin Neurontin	C	1993	Partial seizures, post-herpetic neuralgia
Lacosamide Vimpat	D	2008	Partial seizures
Lamotrigine Lamictal	A	1994	Partial and generalized tonic-clonic seizures, bipolar disorder
Levetiracetam Keppra	C	1999	Partial, generalized tonic-clonic, and myoclonic seizures
Methsuximide Celontin	E	1957	Absence seizures
Oxcarbazepine Trileptal	D	2000	Partial seziures
Perampanel Fycompa	E	2012	Partial and generalized tonic-clonic seizures
Phenobarbital Luminal	A	1916	Partial and generalized seizures, anxiety, and irritable bowel syndrome
Phenytoin Dilantin	A	1938	Generalized tonic-clonic and partial onset seizures, status epilepticus
Pregabalin Lyrica	C	2004	Partial seizures, fibromyalgia, and neuropathic pain
Primidone Mysoline	E*	1954	Partial and generalized tonic-clonic seizures
Rufinamide Banzel	E*	2008	Seizures associated with Dravet syndrome
Stiripentol Diacomit	E	2018	Seizures associated with Dravet syndrome
Tiagabine Gabitril	E	1997	Partial seizures
Topiramate Topamax	C	1996	Partial and generalized tonic-clonic seizures, migraine headaches
Valproate Depakene	A	1978	Absence and complex partial seizures
Vigabatrin Sabril	D	2009	Refractory, complex partial seizures, and infantile spasms

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Zonisamide Zonegran	D	2000	Partial seizures

* Underlined Name indicates the availability of a LiverTox record.

ANNOTATED BIBLIOGRAPHY

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(Textbook of pharmacology and therapeutics).

Wallace SJ. A comparative review of the adverse effects of anticonvulsants in children with epilepsy. Drug Saf 1996; 15: 378-93. PubMed PMID: 8968693.

(Systematic review; ALT elevations occur in 4% of children on phenytoin, 6% on valproate, 1% on carbamazepine and rarely with tiagabine or gabapentin; no mention of hepatotoxicity of topiramate).

Hamer HM, Morris HH. Hypersensitivity syndrome to antiepileptic drugs: a review including new anticonvulsants. Clevel Clin J Med 1999; 66: 239-45. PubMed PMID: 10199060.

(Clinical review: hypersensitivity occurs in 1 to 5 per 10,000 users with a higher risk in African Americans and affected siblings; liver involvement common, but most cases are anicteric; other manifestations include facial edema, lymphadenopathy, bone marrow aplasia, pseudolymphoma, thyroiditis, interstitial nephritis; switching to valproate and benzodiazepines is safe, levetiracetam is also an option).

Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, Mason A, et al. Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation. Health Technol Assess 2005; 9: 1-157, iii-iv. PubMed PMID: 15842952.

(Extensive systematic review of anticonvulsant medications including assessment of serious, rare and long term adverse events; focusing on gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate and vigabatrin).

LaRoche SM. A new look at the second-generation antiepileptic drugs: a decade of experience. Neurologist 2007; 13: 133-9. PubMed PMID: 17495757.

(Review of second generation anticonvulsants approved since 1994 including felbamate, gabapentin, lamotrigine, pregabalin, topiramate, tiagabine, levetiracetam, oxcarbazepine and zonisamide; Stevens-Johnson syndrome is associated with lamotrigine and oxcarbazepine, no mention of liver toxicity from the other agents).

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, valproate accounted for 6, lamotrigine 5, phenytoin 5, gabapentin and topiramate 1 each, but details not provided).

Björnsson E. Hepatotoxicity associated with antiepileptic drugs. Acta Neurol Scan 2008; 118: 281-90. PubMed PMID: 18341684.

(Review of anticonvulsant induced liver injury).

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 including 13 [10%] due to anticonvulsants: phenytoin 8, carbamazepine 3 and valproate 2).

Ferrajolo C, Capuano A, Verhamme KM, Schuemie M, Rossi F, Stricker BH, Sturkenboom MC. Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. Br J Clin Pharmacol 2010; 70: 721-8. PubMed PMID: 21039766.

(World wide pharmacovigilance database contained 9036 hepatic adverse drug reactions in children, 7 anticonvulsants were listed among the top 41 causes: valproate [208 cases, ranking 3rd] carbamazepine [140, 4th], lamotrigine [112, 7th], phenytoin [57, 20th], topiramate [51, 22nd], oxcarbazepine [43, 28th], phenobarbital [41, 32nd]).

Devarbhavi H, Karanth D, Prasanna KS, Adarsh CK, Patil M. Drug-Induced liver injury with hypersensitivity features has a better outcome: a single-center experience of 39 children and adolescents. Hepatology 2011; 54: 1344-50. PubMed PMID: 21735470.

(Among 39 children with drug induced liver disease seen at a single referral center in India between 2005 and 2010, 10 cases were due to phenytoin and 6 to carbamazepine, all of whom survived in contrast to deaths of 12 of 23 children with hepatocellular injury without signs of hypersensitivity [largely due to antituberculosis medications]).

Molleston JP, Fontana RJ, Lopez MJ, Kleiner DE, Gu J, Chalasani N; for the Drug-Induced Liver Injury Network. Characteristics of idiosyncratic drug-induced liver injury in children: results from the DILIN Prospective Study. J Pediatr Gastroenterol Nutr 2011; 53: 182-9. PubMed PMID: 21788760.

(Among 30 children with drug induced liver injury enrolled in a prospective US database between 2004 and 2008, 8 were due to anticonvulsants [lamotrigine in 3, valproate in 3, phenytoin in 1 and carbamazepine in 1], none of which were fatal or led to chronic injury).

Kwon H, Lee SH, Kim SE, Lee JH, Jee YK, Kang HR, Park BJ, Park JW, Hong CS. Spontaneously reported hepatic adverse drug events in Korea: multicenter study. J Korean Med Sci 2012; 27: 268-73. PubMed PMID: 22379337.

(Summary of 2 years of adverse event reporting in Korea; of 9360 reports, 567 were liver related, including 55 [10%] attributed to anticonvulsants: 33 to valproate, 8 topiramate, 6 carbamazepine, 2 lamotrigine, 2 gabapentin and 1 phenytoin).

Drugs for epilepsy. Treat Guidel Med Lett 2013; 11: 9-18. PubMed PMID: 23348233.

(Concise review of drugs of choice for epilepsy with discussion of clinical indications, adverse effects).

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, including 3 attributed to anticonvulsants: 2 due to phenytoin and 1 to gabapentin).

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.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, 7 of which were due to anticonvulsants: 3 due to valproate, 3 phenytoin and 1 carbamazepine).

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. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 40 [4.5%] were attributed to anticonvulsant agents including 12 to phenytoin, 9 lamotrigine, 7 valproic acid, 4 carbamazepine, 3 gabapentin, 2 topiramate, 1 pregabalin, 1 ethosuximide, and 1 fosphenytoin).

Drugs for epilepsy. Med Lett Drugs Ther 2017; 59 (1526): 121-30. PubMed PMID: 28746301.

(Concise review of the drugs available for therapy of epilepsy including brief summary of adverse events with each).

Vidaurre J, Gedela S, Yarosz S. Antiepileptic drugs and liver disease. Pediatr Neurol 2017; 77: 23-36. PubMed PMID: 29097018.

(Review of the use of anticonvulsants in patients with liver disease recommends use of agents that have little hepatic metabolism such as levetiracetam, lacosamide, topiramate, gabapentin and pregabalin, lacosamide being a good choice because of linear pharmacokinetics, only partial hepatic metabolism, with inactive metabolites and lack of clinically significant CYP450 interactions).