U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Valproate. [Updated 2013 Nov 26].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Valproate

Updated: November 26, 2013.

OVERVIEW

Introduction

Valproate or valproic acid is a branched chain organic acid that is used as therapy of epilepsy, bipolar disorders and migraine headaches and is a well known cause of several distinctive forms of acute and chronic liver injury.

Background

Valproate (val proe' ate) is a carboxylic acid derivative that appears to act by increasing brain levels of gamma aminobutyric acid (GABA), the major inhibitory neurotransmitter in the human brain. Valproate has been shown to be effective in several forms of seizures. Valproate was approved for therapy of epilepsy in adults and children in 1978 and is currently one of the major anticonvulsant medications used. Current approved uses include both monotherapy and in combination with other anticonvulsants for complex absence seizures, complex partial seizures and mixed seizure types. Valproate is also used for prevention of migraine headaches and for bipolar disorders. The recommended dose of valproate varies by indication. The initial recommended dose for therapy of seizures is 10 to 15 mg/kg/day, with increases of 5 to 10 mg/kg/day weekly to achieve an optimal clinical response. Monitoring of drug levels is often recommended. Valproate is available in multiple generic and brand formulations as capsules, tablets and syrups and in delayed release forms of 125, 250 and 500 mg. Oral forms also include divalproex, which dissociates into valproate in the gastrointestinal tract and is available in capsules of 125 mg under the brand name Depakote. Valproate sodium is also available in parenteral formulations. Valproate has multiple side effects and clinically significant drug interactions; common side effects include headache, insomnia, nervousness, somnolence, tremor, blurred vision, nausea, weight gain and rash.

Hepatotoxicity

Prospective studies suggest that 5% to 10% of persons develop ALT elevations during long term valproate therapy, but these abnormalities are usually asymptomatic and can resolve even with continuation of drug. Unlike phenytoin and carbamazepine, valproate does not induce elevations in serum GGT levels. More importantly and not uncommonly, valproate can cause several forms of clinically apparent hepatotoxicity. Indeed, more than 100 fatal cases of acute or chronic liver injury due to valproate have been reported in the literature. Three clinically distinguishable forms of hepatotoxicity (besides simple aminotransferase elevations) can occur with valproate.

The first syndrome is hyperammonemia with minimal or no evidence of hepatic injury. This syndrome typically presents with progressive and episodic confusion followed by obtundation and coma. The time to onset is often within a few weeks of starting valproate or increasing the dose, but it can present months or even years after starting the medication (Case 1). The diagnosis is made by the finding of elevations in serum ammonia with

normal (or near normal) serum aminotransferase and bilirubin levels. Valproate levels are usually normal or minimally high. The syndrome resolves within a few days of stopping valproate, but may reverse more rapidly with carnitidine supplementation or renal hemodialysis.

The second form of injury from valproate is an acute hepatocellular injury with jaundice, typically accompanied by hepatocellular or mixed pattern of enzyme elevations (Case 2). This acute liver injury pattern usually has its onset within 1 to 6 months of starting valproate. The pattern of serum enzyme elevations can be hepatocellular or mixed; sometimes the serum aminotransferase levels are not markedly elevated, despite the severity of injury.

Immunoallergic features (fever, rash, eosinophilia) are usually absent, but rare cases with prominent features of hypersensitivity have been reported (Case 3). Multiple instances of fatal acute hepatic failure due to valproate have been published and valproate is regularly listed as a cause of drug induced acute liver failure. Liver histology is distinctive and reveals a microvesicular steatosis with central lobular necrosis, mild to moderate inflammation and cholestasis. In cases with a prolonged course, fibrosis, bile duct proliferation and regenerative nodules may be present. Prospective studies using historical controls suggest that carnitidine (particularly intravenously) may be beneficial if given soon after presentation.

The third form of hepatic injury due to valproate is a Reye-like syndrome described in children on valproate who develop fever and lethargy (suggestive of a viral infection) followed by confusion, stupor and coma, with raised ammonia levels and marked ALT elevations but normal or minimally elevated bilirubin levels. Metabolic acidosis is also common and the syndrome can be rapidly fatal. Valproate may simply be an aspirin-like agent capable of triggering Reye syndrome if it is being taken when the child develops either influenza or varicella infection.

All three forms of valproate hepatotoxicity have features of mitochondrial injury and liver histology, and usually demonstrates microvesicular steatosis with variable amounts of inflammation and cholestasis. Young age (<2 years), presence of other neurological conditions and concurrent use of other anticonvulsants appear to be important risk factors for acute liver failure due to valproate. Valproate has been rarely associated with anticonvulsant hypersensitivity syndrome and generally is a safe alternative in patients with that syndrome caused by the aromatic anticonvulsants.

Mechanism of Injury

The mechanism of valproate hepatotoxicity is thought to be due to mitochondrial toxicity, perhaps from inhibition of beta oxidation and subsequent loss of mitochondrial function. Valproate is extensively metabolized by the liver and excreted in urine. Valproate therapy lowers tissue carnitine levels which may affect mitochondrial function and cause the hyperammonemia and microvesicular steatosis. Genetic factors also appear to be important, as valproate hepatotoxicity is more common in patients who are heterozygous for mutations in gamma polymerase, the predominant DNA polymerase found in mitochondria. Children with the Alpers-Huttenlocher syndrome who are homozygous for this mutation are at very high risk of developing valproate hepatotoxicity which is often fatal and responds poorly to liver transplantation. Alpers syndrome is characterized by progressive cerebral degeneration, seizures and cirrhosis and has been shown to be due to mutations in the gene for polymerase gamma, the enzyme responsible for mitochondrial DNA replication. Indeed, valproate is considered contraindicated in children with known or suspected Alpers-Huttenlocher syndrome.

Outcome and Management

Valproate hepatotoxicity varies in severity from minimal and asymptomatic ALT elevations to severe liver injury with progressive jaundice, hepatic synthetic dysfunction, coma and death. Monitoring of symptoms and serum aminotransferase levels is recommended for children for the first 6 months of valproate therapy. Valproate has not been associated with vanishing bile duct syndrome, but cases of cirrhosis with severe fibrosis have been

attributed to chronic indolent hepatotoxicity from valproate. Importantly, carnitidine appears to be a specific antidote for valproate hepatotoxicity and studies in animal models and human studies with historical controls suggest that prompt administration of carnitine (particularly when given intravenously) improves survival in acute valproate hepatotoxicity. Oral carnitine was approved for use in valproate toxicity in 1992 and an intravenous formulation in 1996. The typically recommended dose is 100 mg/kg intravenously over 30 minutes (but less than 6 grams), followed by 15 mg/kg every four hours until clinical improvement.

Drug Class: Anticonvulsants

CASE REPORTS

Case 1. Hyperammonemia due to valproate.

[Modified from a case in the database of the Drug-Induced Liver Injury Network]

A 47 year old woman with left frontal astrocytoma was admitted to the hospital for a syncopal episode and control of seizures. She was being treated with phenobarbital, valproate and levetiracetam. While hospitalized she was started on irradiation for her brain tumor. After a month in the hospital, her seizures were reasonably well controlled, but she developed unexplained somnolence and confusion. Liver tests were not abnormal, but serum ammonia levels were markedly elevated. Valproate was stopped and her mental status improved rapidly, ammonia levels decreasing into the normal range within 3 days. She subsequently improved and was discharged two weeks later.

Key Points

Medication:	Valproate (450 mg/day)
Pattern:	(R=not applicable)
Severity:	1+ (no jaundice)
Latency:	3 months
Recovery:	4 days
Other medications:	Phenobarbital, levetiracetam, phenergan (all were continued)

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Ammonia (µmol/L)	Other
0		Valproate started: 500 mg daily				
60 days		15	50	0.4		Hospital admission
80 days		15	58	0.2		
90 days	0	28	59	0.1	286	
91 days	1 days				362	Valproate stopped
92 days	2 days				70	
93 days	3 days				36	
96 days	6 days	74	74	0.1	20	
103 days	13 days	90	155	0.3	37	
Normal Values		**<42**	**<115**	**<1.2**		

Comment

A woman on multiple anticonvulsants developed somnolence and confusion during a prolonged hospitalization during which she was receiving radiation for a brain astrocytoma. While there were other possible reasons for her change in mental status, astute physicians tested her blood ammonia level, which was markedly elevated. Withdrawal of valproate led to a prompt improvement. This case represents the hyperammonemia of valproate that typically occurs without other evidence of hepatitis injury, although hyperammonemia is believed to be caused by the effects of valproate on hepatic mitochondrial function.

Case 2. Acute liver failure due to valproate.

[Modified from a case in the database of the Drug-Induced Liver Injury Network]

A 15 year old adolescent male with seizures being treated with valproate was admitted to the hospital having developed jaundice after a three week history of fatigue and body aches. He had developed seizures at age 9 and was treated with phenytoin for several years, but was switched to valproate (750 mg/day) because of reappearance of seizures approximately 4 months before admission. Three weeks before admission, he developed an influenza-like illness with fever, fatigue, body aches and diarrhea. The diarrhea resolved, but fatigue persisted. He was seen for evaluation and found to have elevations in liver tests. He was treated with azithromycin, but continued to do poorly developing behavioral changes and then jaundice. Valproate was stopped, and he was admitted to the hospital 4 days later because of worsening jaundice and confusion. On examination, he was disoriented and jaundiced but without signs of chronic liver disease, rash or fever. Serum bilirubin was 11.5 and INR 4.1 (Table). He was placed in intensive care. Tests for hepatitis A, B and C and autoantibody tests were negative, and serum ceruloplasmin and copper were normal. An abdominal ultrasound showed no evidence of biliary obstruction. His hepatic failure worsened and he was transferred to a liver transplant center, undergoing liver transplantation ~3 weeks after his initial admission.

Key Points

Medication:	Valproate (250→750 mg/day)
Pattern:	Mixed (R=4.3)
Severity:	5+ (acute liver failure requiring liver transplantation)
Latency:	3 months
Recovery:	No
Other medications:	Azithromycin

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
0		Valproate started: 250 mg raised to 750 mg daily			
3.5 months	-3 weeks	287	441	1.4	Given azithromycin
	0	248	423	3.1	
4 months	5 days	240	401	15.2	Admission: INR 4.1
	8 days	147	267	15.5	
	15 days	89	161	23.8	
5 months	22 days	51	237	26.7	Liver transplantation
Normal Values		**<42**	**<115**	**<1.2**	

Comment

Acute liver failure due to valproate hepatotoxicity. The latency period of 3 months and only moderate elevation in serum aminotransferase levels are typical of the acute hepatotoxicity from valproate. The explant showed massive hepatic necrosis with regenerative areas and mild fibrosis. The incubation period to onset of valproate hepatotoxicity is usually 1 to 3 months. Symptoms developing during this period should lead to a prompt discontinuation of valproate and administration of carnitine. In this instance, the history of a viral-like illness immediately before the onset of liver injury suggests a Reye-like syndrome. However, the clinical course and outcome were more typical of the acute hepatitis-like syndrome caused by valproate.

Case 3. Drug rash with eosinophilia and acute liver failure due to valproate.

[Modified from: van Zoelen MA, de Graaf M, van Dijk MR, Bogte A, van Erpecum KJ, Rockmann H, Maarschalk-Ellerbroek LJ. Valproic acid-induced DRESS syndrome with acute liver failure. Neth J Med 2012; 70: 155. PubMed Citation]

A 26 year old man developed fever, rash and lymphadenopathy 1.5 months after starting valproic acid (500 mg twice daily) because of seizures arising after an intracerebral bleed. He had no history of liver disease, alcohol abuse, drug allergies or risk factors for viral hepatitis. His other medications included baclofen (500 mg three times daily), clemastine (2 mg twice daily) and acetaminophen (1 gram four times daily). Upon presentation, physical examination revealed a generalized papular-pustular rash, facial edema, lymphadenopathy and scleral icterus. Laboratory testing showed a total serum bilirubin of 10.5 mg/dL (direct 6.7 mg/dL), ALT 2800 U/L, AST 1219 U/L, alkaline phosphatase 456 U/L, GGT 216 U/L and prothrombin time 21.6 seconds. Acetaminophen levels were undetectable and valproate levels were "subtherapeutic". Tests for viral hepatitis and autoimmune conditions were unrevealing. Abdominal ultrasound demonstrated enlargement of the liver and spleen but no evidence of biliary obstruction. A skin biopsy was compatible with a drug-induced hypersensitivity rash. Valproate and acetaminophen were stopped upon admission and the seizure disorder was managed with levetiracetam. Prednsione was started and the skin rash, lymphadenopathy and facial edema resolved rapidly. Symptoms resolved within 6 weeks and laboratory tests returned to normal by 15 weeks, at which point prednisolone was stopped.

Key Points

Medication:	Valproic acid (500 mg, twice daily)
Pattern:	Hepatocellular (R=17)
Severity:	4+ (jaundice and prolonged prothrombin time)
Latency:	1.5 months
Recovery:	15 weeks
Other medications:	Acetaminophen, baclofen, clemastine

Comment

A man with recent onset of seizures developed the syndrome of drug-rash with eosinophilia and systemic symptoms (DRESS) within 6 weeks of starting valproic acid. He had fairly severe liver injury with jaundice and prolongation of the prothrombin time, but without other evidence of hepatic failure (encephalopathy or ascites). He responded rapidly upon discontinuation of the valproate and institution of prednisolone. DRESS syndrome is well known to occur with aromatic anticonvulsant therapy (phenytoin, phenobarbital, carbamazepine, lamotrigine), but is rare with valproate therapy alone. DRESS and Stevens Johnson syndrome have also been linked to acetaminophen therapy, but quite rarely. In this instance, acetaminophen may have contributed to the

severity of liver injury but was probably not primarily responsible. While this case report lacked some necessary information (eosinophil count, hepatitis virus serology, autoimmune marker testing), it is fairly convincing and demonstrates the wide variability in clinical presentation of valproate induced liver injury.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Valproate – Depakene®, Depakote®

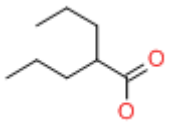
DRUG CLASS

Anticonvulsants

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Valproate	99-66-1	C8-H16-O2	

ANNOTATED BIBLIOGRAPHY

Selected References updated: 26 November 2013

Zimmerman HJ. Anticonvulsants. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999: pp. 498-516.

(Expert review of valproate and liver injury published in 1999, estimated to occur in ~1:5,000 patients, more frequent in infants <2 years, onset insidious after 1-4 months of treatment [range 3 days-2 years], typically with ALT 3-25 times ULN, and with microvesicular steatosis and centrolobular necrosis on biopsy; high fatality rate).

Pirmohamed M, Leeder SJ. Anticonvulsant agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013: pp 423-41.

(Review of anticonvulsant induced liver injury mentions that the onset of liver injury from valproate is typically after 1 to 3 months, but is variable and instances of onset within days and after years of use have been published).

McNamara JO. Pharmacology of the epilepsies. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 583-608.

(Textbook of pharmacology and therapeutics).

Huttenlocher PR, Solitare GB, Adams G. Infantile diffuse cerebral degeneration with hepatic cirrhosis. Arch Neurol. 1976; 33: 186-92. PubMed PMID: 1252162.

(Description of 4 children [2 pair of siblings] who developed developmental delay and seizures starting between 1 and 3 years of age and progressing to disability and death in infancy, often with evidence of steatosis and cirrhosis, which is now often called Alpers-Huttenlocher syndrome [AHS]).

Sackellares JC, Lee SI, Dreifuss FE. Stupor following administration of valproic acid to patients receiving other antiepileptic drugs. Epilepsia 1979; 20: 697-703. PubMed PMID: 115681.

(4 cases of stupor due to valproate; 2 men and 2 women, ages 8 to 37 years, with onset 2-30 days after valproate added to other anticonvulsants, resolving in 3-7 days after stopping; normal valproate levels, ammonia levels not tested).

Suchy FJ, Balistreri WF, Buchino JJ, Sondheimer JM, Bates SR, Kearns GL, Stull JD, Bove KE. Acute hepatic failure associated with the use of sodium valproate. Report of two fatal cases. N Engl J Med 1979; 300: 962-6. PubMed PMID: 372803.

(Two fatal cases of valproate induced liver injury arising 6 and 8 weeks after starting valproate in 5 and 11 year olds [bilirubin 7.0 rising to 31 and 2.6 to 22 mg/dL, ALT 58 and 280 U/L, Alk P 15.7 and 500 U/L], autopsies showing submassive necrosis and microvesicular steatosis).

Donat JF, Bocchini JA Jr, Gonzalez E, Schwendimann RN. Valproic acid and fatal hepatitis. Neurology 1979; 29: 273-4. PubMed PMID: 372842.

(17 month old child with seizures developed jaundice one month after starting valproate [bilirubin 4.4 mg/dL, AST 130 U/L, ammonia 266 IU/L], progressing to hepatic failure and death one week later, autopsy showing changes suggestive of "viral or drug-induced hepatitis").

Mathis RK, Hanson RF, Sharp HL. Hepatic failure from valproic acid. N Engl J Med 1979; 301: 436. PubMed PMID: 379647.

(Letter in response to Suchy [1979] argues for mitochondrial injury as the cause of valproate hepatotoxicity, in that electron microscopy of liver biopsies from two children showed enlarged mitochondria with decreased matrix density, altered cristae, and increase in dense bodies).

Gerber N, Dickinson RG, Harland RC, Lynn RK, Houghton LD, Antonias JI, Schimschock JC. Reye-like syndrome associated with valproic acid therapy. J Pediatr 1979; 95: 142-4. PubMed PMID: 383927.

(12 year old girl developed fatigue and fever followed by progressive coma 2 months after starting valproate [bilirubin 1.3 mg/dL, ALT 78 U/L, prothrombin time 17 sec, ammonia 204 µmol/L], with acidosis, progressive coma and death; autopsy showing microvesicular fat in hepatocytes and renal tubular cells and centrolobular necrosis indicative of Reye syndrome).

Jacobi G, Thorbeck R, Ritz A, Janssen W, Schmidts HL. Fatal hepatotoxicity in child on phenobarbitone and sodium valproate. Lancet 1980; 1 (8170): 712-3. PubMed PMID: 6103126.

(7 year old boy developed lethargy followed by coma 3 months after starting valproate [bilirubin rising to 17.5 mg/dL, ALT 60 U/L, ammonia 455 µmol/L], with acidosis and death, autopsy showing hepatic steatosis, centrolobular necrosis and cholestasis).

Ware S, Millward-Sadler GH. Acute liver disease associated with sodium valproate. Lancet 1980; 2 (8204): 1110-3. PubMed PMID: 6107726.

(Five patients with valproate hepatotoxicity; 4 children, ages 2-9 years, treated with valproate for 3 to 5 months, developed acute liver injury, autopsies showing acute hepatic necrosis and microvesicular steatosis).

Sodium valproate and the liver. Lancet 1980; 2 (8204): 1119-20. PubMed PMID: 6107730.

(Editorial in response to Ware [1980] commenting on the many reports of fatal valproate hepatotoxicty in young children with features of Reye syndrome).

Le Bihan G, Bourreille J, Sampson M, Leroy J, Szekely AM, Coquerel A. Fatal hepatic failure and sodium valproate. Lancet 1980; 2 (8207): 1298-9. PubMed PMID: 6108469.

(17 year old girl developed fatigue 3 months after starting valproate [bilirubin 1.9 mg/dL, ALT 161 U/L, Alk P 190 U/L, prothrombin time 20 sec], with progressive hepatic failure, ascites, encephalopathy and liver transplant 1 month later).

Young RS, Bergman I, Gang DL, Richardson EP Jr. Fatal Reye-like syndrome associated with valproic acid. Ann Neurol 1980; 7: 389. PubMed PMID: 6769385.

(8 year old boy developed worsening seizures, fever and stupor 3 weeks after starting valproate [bilirubin not given, AST 564 U/L, ammonia 354 ug/dL], with hypoglycemia, acidosis and death within days, autopsy showing microvesicular fat in liver and renal tubules).

Coulter DL, Allen RJ. Hyperammonemia with valproic acid therapy. J Pediatr 1981; 99: 317-9. PubMed PMID: 6788925.

(Among "several hundred" children being treated with valproate, 11 developed stupor or coma, 8 of whom had elevated ammonia levels [mean 118.2 µmol/L], six of whom had normal liver tests and recovered within 1-3 days of stopping valproate, some tolerating lower doses).

Gastaut H, Noel P. A case of fatal toxic hepatitis: recommendations for the administration of sodium valproate. Epilepsia 1981; 22: 711-3. PubMed PMID: 6796404.

(2 year old boy developed stupor and coma 5 months after starting valproate [bilirubin 3 mg/dL, ALT 1975 U/L, ammonia 132 µg/dL], with progressive liver failure and death 5 days later, autopsy showing "ballooned hepatocytes with a clear cytoplasm but no steatosis").

Zimmerman HJ, Ishak KG. Valproate-induced hepatic injury: analyses of 23 fatal cases. Hepatology 1982; 2: 591-7. PubMed PMID: 6811394.

(Review of 23 fatal cases of valproate liver injury: ages 1-28 years, 56% male, onset after <1 to 4 months of 13-71 mg/kg/day; most patients were taking other anticonvulsants; symptoms were fatigue followed by jaundice, ascites and coma; no rash or eosinophilia; ALT levels were usually <300 U/L, AST>ALT, bilirubin 1.0-36 mg/dL, protime and ammonia usually elevated. Histology showed microvesicular steatosis, centrizonal and ballooning necrosis; some patients already had cirrhosis).

Zafrani ES, Berthelot P. Sodium valproate in the induction of unusual hepatotoxicity. Hepatology 1982; 2: 648-9. PubMed PMID: 6811395.

(Editorial in response to Zimmerman and Ishak [1982] describing 31 fatal cases from Europe, ages 9 months to 29 years, twice as common in children than adults, no rash or eosinophilia, onset with vomiting and weakness, jaundice late, ALT not very high, histology showing fat and centrilobular necrosis).

Stricker BH. [Liver damage caused by valproic acid]. Ned Tijdschr Geneeskd 1982; 126: 2111-3. Dutch. PubMed PMID: 6817146.

(Review of valproate hepatotoxicity, mentioning that there have been at least 50 fatal cases reported in the literature, clinical features can resemble Reye syndrome and liver histology reveals microvesicular steatosis and centrolobular necrosis).

Ohtani Y, Endo F, Matsuda I. Carnitine deficiency and hyperammonemia associated with valproic acid therapy. J Pediatr 1982; 101: 782-5. PubMed PMID: 6813444.

(Testing of 14 patients on valproate and 11 on other anticonvulsants for carnitine levels reported low levels in those on valproate [33 vs 49 nM], correlating with dose and with ammonia levels; carnitine supplementation was associated with rapid decrease in ammonia levels, from 144 to 71 µg/dL).

Itoh S, Yamaba Y, Matsuo S, Saka M, Ichinoe A. Sodium valproate-induced liver injury. Am J Gastroenterol 1982; 77: 875-9. PubMed PMID: 6814241.

(37 year old woman developed fever and abdominal pain 1 month after starting valproate [bilirubin 2.2 mg/dL, ALT 1550 U/L, Alk P 206 U/L], with rapid improvement upon stopping and sharp rise in rise in bilirubin and ALT within one day of rechallenge; liver biopsy showed microvesicular steatosis, cystalline inclusions in mitochondria and marked centrilobular necrosis).

Zaret BS, Beckner RR, Marini AM, Wagle W, Passarelli C. Sodium valproate-induced hyperammonemia without clinical hepatic dysfunction. Neurology 1982; 32: 206-8. PubMed PMID: 6798491.

(3 cases of hyperammonemia in adults taking valproate, ages 20-51 years, onset days to years after starting, ammonia 56-146 μM, rapid reversal with stopping).

Böhles H, Richter K, Wagner-Thiessen E, Schafer H. Decreased serum carnitine in valproate induced Reye syndrome. Eur J Pediatr 1982; 139: 185-6. PubMed PMID: 6819143.

(3 year old girl developed fatal liver injury ~3 months after starting valproate [bilirubin 4.3 rising to 23 mg/dL, ALT 34 to 82 U/L, Alk P 350 U/L, ammonia 89 μg/dL, glucose 23 mg/dL, low carnitine levels and abnormal valproate metabolites]; hypothesized that injury was due to carnitine deficiency related inhibition of mitochondrial beta oxidation).

Sugimoto T, Nishida N, Yasuhara A, Ono A, Sakane Y, Matsumura T. Reye-like syndrome associated with valproic acid. Brain Dev 1983; 5: 334-7. PubMed PMID: 6412580.

(13 year old girl on chronic valproate therapy had seizures and was admitted in shock with high serum ammonia 400 μM, ALT 1454 U/L, bilirubin 1.2 mg/dL, LDH 29,184 U/L, died 3 days later; questioned whether it was due to Reyes syndrome vs ischemic hepatitis).

de Wolff FA, Peters AC, van Kempen GM. The effects of valproic acid on liver function. Arch Toxicol Suppl. 1983; 6: 369-73. PubMed PMID: 6138013.

(Serum levels of GGT were not elevated in 32 children with epilepsy being treated with valproate).

Perucca E, Hedges A, Makki KA, Ruprah M, Wilson JF, Richens A. A comparative study on the relative enzyme inducing properties of anticonvulsant drugs in epileptic patients. Br J Clin Pharmac 1984; 18: 401-10. PubMed PMID: 6435654.

(Cross sectional study of antipyrine clearance in 122 patients with epilepsy, found dose dependent increase in clearance in those on phenytoin, phenobarbital and carbamazepine, but not on valproate).

Keene DL, Humphreys P, Carpenter B, Fletcher JP. Valproic acid producing a Reye-like syndrome. J Canad Sci Neurol 1982; 435-7. PubMed PMID: 6817907.

(3 year old boy with severe seizure disorder and status epilepticus developed coma and acute liver failure on valproate [2 years], phenytoin and ethosuximide with AST >4500 U/L, normal bilirubin and valproate levels; subsequently had worsening neurological status, liver biopsy showing macro and microvesicular fat, ballooning, cholestasis and inflammation, similar but not completely typical of Reyes syndrome).

Coulter DL. Carnitine deficiency: a possible mechanism for valproate hepatotoxicity. Lancet 1984; 1: 689. PubMed PMID: 6142383.

(Letter in which author proposes that valproate lowers carnitine levels, which impairs metabolism of fatty acids and mitochondrial function causing hyperammonemia and liver injury, recommends supplementation).

Green SH. Sodium valproate and routine liver function tests. Arch Dis Child 1984; 59: 813-4. PubMed PMID: 6435543.

(Editorial suggesting that monitoring liver tests is unlikely to be helpful in predicting idiosyncratic reactions to valproate).

Powell-Jackson PR, Tredger JM, Williams R. Hepatotoxicity to sodium valproate: a review. Gut 1984; 25: 673-81. PubMed PMID: 6428980.

(Review of literature and own cases of valproate liver injury; describe three forms, hepatitis-like syndrome arising 4-16 weeks after starting therapy with high fatality rate; a Reyes-like syndrome and hyperammonemia with minimal liver injury).

Murphy JV, Marquardt KM, Shug AL. Valproic acid associated abnormalities of carnitine metabolism. Lancet 1985; 1: 820-1. PubMed PMID: 2858698.

(6 month old infant with Reyes-like syndrome [ALT 9690 U/L] had low carnitine levels that increased with recovery; testing 13 asymptomatic children on valproate found low levels ~40 μM compared to 50 μM in controls).

Blaw ME, Belknap WM. Valproate hepatotoxicity. Pediatr Neurol 1985; 1: 320. PubMed PMID: 3939748.

(Report a fatal case of valproate hepatotoxicity [no specific information given], recommending prompt investigation if symptoms develop on valproate, particularly during first month of therapy).

Dickinson RG, Bassett ML, Searle J, Tyrer JH, Eadie MJ. Valproate hepatotoxicity: a review and report of two instances in adults. Clin Exp Neurol 1985; 21: 79-91. PubMed PMID: 3939614.

(Review of literature and 2 case reports; 19 year old male with drowsiness starting 2 months after increasing valproate dose [bilirubin ~5.0 mg/dL, AST 3x ULN, Alk P ~4x ULN], resolving rapidly upon stopping; 25 year old man with liver injury arising 1 month after starting valproate with biopsy showing centrolobular necrosis).

Møller P, Henriksen O. [Severe liver involvement during use of sodium valproate]. Tidsskr Nor Laegeforen 1986; 106: 940-1. Norwegian. PubMed PMID: 3088761.

(27 year old man developed agitation within days of starting valproate [ALT 313 U/L, bilirubin and Alk P normal], which rapidly improved on stopping, but the patient died suddenly 6 weeks later).

Ratnaike RN, Schapel GJ, Purdie G, Rischbieth RHC, Hoffmann S. Hyperammonaemia and hepatotoxicity during chronic valproate therapy: enhancement by combination with other antiepileptic drugs. Br J Clin Pharmac 1986; 22: 100-3. PubMed PMID: 3091053.

(Cross sectional analysis of ammonia levels and liver tests in 81 patients with epilepsy; higher average levels of ammonia in patients on valproate [37.1 vs 28.7 μmol], slightly higher rate of elevations in those receiving other agents [phenytoin, carbamazepine] as well).

Colletti RB, Trainer TD, Krawisz BR. Reversible valproate fulminant hepatic failure. J Pediatr Gastroenterol Nutr 1986; 5: 990-4. PubMed PMID: 3098946.

(12 year old boy developed fever and rash followed by confusion 2-3 months after starting valproate [bilirubin 4.6 mg/dL, ALT 2425 U/L, Alk P 289 U/L, ammonia 66 μmol/L, prothrombin time 15 sec], improvement beginning a week after stopping, values ultimately normal; liver biopsy showing microvesicular steatosis and focal necrosis).

Laub MC, Paetzke-Brunner I, Jaeger G. Serum carnitine during valproic acid therapy. Epilepsia 1986; 7: 559-62. PubMed PMID: 3093213.

(Cross sectional study of 21 patients on valproate, 21 on other anticonvulsants, and 21 controls; found lower carnitine levels in patients on valproate, but small differences and no response in one patient with fatal hyperammonemia).

Dreifuss FE. Fatal liver failure in children on valproate. Lancet 1987; 1: 47-8. PubMed PMID: 2879132.

(Letter pointing out safety of valproate if used in children above the age of 2, without familial history of liver disease, in low doses without concurrent aspirin or during febrile illness and rapid investigation of symptoms).

Schneffer D, König S, Rauterberg-Ruland I, Kochen W, Hofmann WJ, Unkelbach S. Fatal liver failure in 16 children with valproate therapy. Epilepsia 1988; 29: 530-42. PubMed PMID: 3137017.

(Analysis of 16 patients with fatal valproate hepatotoxicity in Germany between 1977 and 1987; ages 1-17, 6 on monotherapy, onset occurred mostly in first 6 months; typical presentation with nausea, abdominal pain and apathy followed by jaundice, biopsies show micro- and macro-vesicular fat and centrilobular necrosis, often with fibrosis; estimated fatality rate 1:5,000, recommended monitoring for first 6 months).

Dreifuss FE, Santilli N, Langer DH, Sweeney KP, Moline KA, Menander KB. Valproic acid hepatic fatalities: a retrospective review. Neurology 1987; 37: 379-85. PubMed PMID: 3102998.

(Review of all the reports of fatal liver injury from valproate reported to drug company and FDA between 1978 and 1984 found 37 cases; highest number in children <2 years, with coincidental neurologic problems and polytherapy with other anticonvulsants; onset usually within first 90 days; variable presentations and laboratory abnormalities).

Iinuma K, Hayasaka K, Narisawa K, Tada K, Hori K. Hyperamino-acidaemia and hyperammonaemia in epileptic children treated with valproic acid. Eur J Pediatr 1988; 148: 267-9. PubMed PMID: 3145882.

(Among 75 children with epilepsy, serum ammonia levels were elevated in 20% [8/41] of those on valproate, but in none of 34 children taking other anticonvulsants).

Dreifuss FE, Langer DH, Moline KA, Maxwell JE. Valproic acid hepatic fatalities. II. US experience since 1984. Neurology 1989; 39: 201-7. PubMed PMID: 2492646.

(During further follow up of national data, there was an increase use of valproate, but a decrease in incidence of valproate hepatotoxicity; thus in 1985-86, only four cases were identified, 3 with polytherapy, 3 in children with other medical conditions, clinical onset occurred after 60-105 days of therapy).

Kuhara T, Inoue Y, Matsumoto M, Shinka T, Matsumoto I, Kawahara N, Sakura N. Markedly increased omega-oxidation of valproate in fulminant hepatic failure. Epilepsia 1990; 31: 214-7. PubMed PMID: 2108017.

(Abnormal metabolites of valproate found in urine of child with fatal Reyes-like syndrome on long term valproate [ALT 5330, LDH 18405, ammonia 212 mg/L and rising bilirubin], abnormalities suggested increase in P-450 metabolism of valproate).

Appleton RE, Farrell K, Applegarth DA, Dimick JE, Wong LT, Davidson AG. The high incidence of valproate hepatotoxicity in infants may relate to familial metabolic defects. Can J Neurol Sci 1990; 17: 145-8. PubMed PMID: 2113424.

(Two unrelated infants developed fatal, acute liver failure after 2-3 days of valproate, both had siblings with developmental delay and liver abnormalities and steatosis not on valproate, suggesting that valproate may not have been responsible for liver injury in the index patients).

Wyllie E, Wyllie R. Routine laboratory monitoring for serious adverse effects of antiepileptic medications: the controversy. Epilepsia 1991; 32 (Suppl 5): S74-9. PubMed PMID: 2113424.

(The effectiveness of monitoring serum enzyme levels in patients starting anticonvulsant therapy in preventing acute liver failure is controversial and unproven; this approach is most appropriate for valproate, but probably only during the first 6 months and in high risk subjects).

Binek J, Hany A, Egloff B, Heer M. [Acute fatal liver insufficiency due to valproic acid therapy]. Schweiz Med Wochenschr 1991; 121: 228-33. German. (21 year old man developed jaundice 12 weeks after starting valproate [bilirubin 10.2 mg/dL, ALT 500 U/L, Alk P 348 U/L, prothrombin index 19%], followed by

progressive multiorgan failure and death; autopsy showing massive necrosis and steatosis PubMed PMID: 2008603.

).

Bell EA, Shaefer MS, Markin RS, Wood RP, Langnas AN, Stratta RJ, Shaw BW Jr. Treatment of valproic acid-associated hepatic failure with orthotopic liver transplantation. Ann Pharmacother 1992; 26: 18-21. PubMed PMID: 1606338.

(23 year old woman developed lethargy and confusion followed by coma 6 weeks after starting valproate [bilirubin 3.1 mg/dL, ALT 10,640 U/L, Alk P 197 U/L, prothrombin time 54 sec, ammonia 127 umol/L], with severe metabolic acidosis and progressive liver failure, undergoing liver transplant within 48 hours of presentation).

Murphy JV, Groover RV, Hodge C. Hepatotoxic effects in a child receiving valproate and carnitine. J Pediatr 1993; 123: 318-20. PubMed PMID: 8345435.

(17 month old child with developmental delay developed severe liver injury arising 9 weeks after starting valproate [bilirubin 2.3 rising to 26.5 mg/dL, ALT 552 U/L, Alk P 360 U/L, prothrombin time 24.7 sec], with progressive hepatic failure and death 6 weeks later, autopsy showing massive necrosis and fibrosis).

Siemes H, Nau H, Schultze K, Wittfoht W, Drews E, Penzien J, Seidel U. Valproate (VPA) metabolites in various clinical conditions of probable VPA-associated hepatotoxicity. Epilepsia 1993; 34: 332-46. PubMed PMID: 8453944.

(Analysis of plasma valproate levels and its metabolites in 470 patients with epilepsy found no consistent level or pattern of metabolites in patients with liver injury compared to those without).

König SA, Simes H, Blaker F, Boenigk E, Gross-Selbeck G, Hanefeld F, Haas N, et al. Severe hepatotoxicity during valproate therapy: an update and report of eight new fatalities. Epilepsia 1994; 35: 1005-15. PubMed PMID: 7925143.

(Review and update of fatal cases of valproate hepatotoxicity from Germany-Switzerland, risk factors were found to be age <2 years and cases were rare in patients above 18 years; onset can occur >6 months after onset, often presenting with worsening seizures, nausea and apathy after a febrile illness).

Plantin P, Cartier H, Le Bihan G, Clouard P, Lellouche F, Leroy JP. [Drug hypersensitivity syndrome during treatment with valproic acid]. Presse Med 1995; 24: 1624. French. PubMed PMID: 8545377.

(41 year old woman developed fever followed by rash 6 weeks after starting valproate [bilirubin 6.0 mg/dL, ALT 559 U/L, eosinophils 20%), resolving within 4 weeks of stopping).

Krähenbühl S, Mang G, Kupferschmidt H, Meier PJ, Krause M. Plasma and hepatic carnitine and coenzyme A pools in a patient with fatal, valproate induced hepatotoxicity. Gut 1995; 37: 140-3. PubMed PMID: 7672665.

(39 year old woman with bipolar disorder developed stupor 4 months after starting valproate [bilirubin 8.5 mg/dL, ALT 35 U/L, prothrombin index 39%, ammonia 75 µmol/L] and deteriorated after a "cardiovascular collapse", dying of multiorgan failure).

Böhles H, Sewell AC, Wenzel D. The effect of carnitine supplementation in valproate-induced hyperammonaemia. Acta Paediatr 1996; 85: 446-9. PubMed PMID: 8740302.

(In an uncontrolled study, carnitine supplementation led to decreases in ammonia levels and increases in free carnitine levels in 14 patients with hyperammonia on valproate).

Bryant AE, Dreifuss FE. Valproic acid hepatic fatalities, III: US experience since 1986. Neurology 1996; 46: 465-9. PubMed PMID: 8614514.

(Third retrospective study of US experience with fatal hepatotoxicity from valproate summaries 29 cases; risk factors were age <2 years and polytherapy [~1:600 treated subjects]; risk decreased with age so that in adults risk is ~1:30,000, but risk in adults also increased with polytherapy).

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 not reported on tiagabine or gabapentin).

Schwabe MJ, Dobyns WB, Burke B, Armstrong DL. Valproate-induced liver failure in one of two siblings with Alpers disease. Pediatr Neurol 1997; 16: 337-43. PubMed PMID: 9258971.

(Siblings with Alpers syndrome developed progressive developmental delay and seizures, one dying of acute liver failure 1 month after starting valproate).

Pessayre D, Mansouri A, Haouzi D, Fromenty B. Hepatotoxicity due to mitochondrial dysfunction. Cell Biol Toxicol 1999; 15: 367-73. PubMed PMID: 10811531.

(Review of the role of mitochondrial dysfunction in drug induced liver injury focusing upon valproate).

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.

(Hypersensitivity occurs in 1-5/10,000 users of aromatic anticonvulsants, higher risk in African Americans and affected siblings; liver involvement common, but most cases anicteric; other manifestations include facial edema, lymphadenopathy, bone marrow aplasia, pseudolymphoma, thyroiditis, interstitial nephritis).

McLaughlin DB, Eadie MJ, Parker-Scott SL, Addison RS, Henderson RD, Hooper WD, Dickinson RG. Valproate metabolism during valproate-associated hepatotoxicity in a surviving adult patient. Epilepsy Res 2000; 41: 259-68. PubMed PMID: 10962217.

(Valproate is a simple branched chain fatty acid, but has complex metabolism undergoing β-oxidation; 33 year old man developed jaundice and marked ALT elevations [~100x ULN] 7 months after starting valproate, initially had high oxo-VPA relative to valproate suggesting impaired β-oxidation and mitochondrial dysfunction; cause or effect unclear).

Picart N, Périole B, Mazereeuw J, Bonafé JL. [Drug hypersensitivity syndrome to valproic acid] Presse Med 2000; 29: 648-50. PubMed PMID: 10780197.

(28 year old woman developed fever and maculo-papular generalized rash 3 weeks after starting valproate with adenopathy, eosinophilia and ALT 176 U/L, but normal bilirubin and Alk P, rapid resolution and positive skin reaction to valproate 4 months later).

Delarue A, Paut O, Guys JM, Montfort MF, Lethel V, Roquelaure B, Pellissier JF, et al. Inappropriate liver transplantation in a child with Alpers-Huttenlocher syndrome misdiagnosed as valproate-induced acute liver failure. Pediatr Transplant 2000; 4: 67-71. PubMed PMID: 10731063.

(3 year old boy developed acute liver failure within a few months of starting valproate for seizures [bilirubin not given; ALT 196 U/L, prothrombin index 24%], with progressive hepatic failure and liver transplantation within 3 weeks of onset, child dying 4 months later of progressive neurological deterioration).

Kayihan N, Nennesmo I, Ericzon BG, Németh A. Fatal deterioration of neurological disease after orthotopic liver transplantation for valproic acid-induced liver damage. Pediatr Transplant 2000; 4: 211-4. PubMed PMID: 10933322.

(13 year old girl with progressive neurologic disease since age 3-5 years developed acute liver failure 5 months after starting valproate leading to liver transplantation, with subsequent rapid neurological deterioration and death 6 months later).

Thomson MA, Lynch S, Strong R, Shepherd RW, Marsh W. Orthotopic liver transplantation with poor neurologic outcome in valproate-associated liver failure: a need for critical risk-benefit appraisal in the use of valproate. Transplant Proc 2000; 32: 200-3. PubMed PMID: 10701024.

(5 children, ages 1 to 4 years, with acute liver failure from valproate [onset after 2-4 months] had poor neurological outcomes after liver transplantation, explant showing microvesicular steatosis and massive necrosis).

Spahr L, Negro F, Rubbia-Brandt L, Marinescu O, Goodman K, Jordan M, Frossard JL, Hadenque A. Acute valproate-associated microvesicular steatosis: could the [13C]methionine breath test be useful to assess liver mitochondrial function? Dig Dis Sci 2001; 46: 2758-61. PubMed PMID: 11768270.

(24 year old woman took an overdose of valproate [~7 grams] and presented with drowsiness and marked rise in ALT and fall in prothrombin over next 2 days, but without jaundice; liver biopsy showed microvesicular steatosis and swollen mitochondria, abnormal C-methionine breath test, rapidly improved).

Chen WT, Yen DJ, Yu HY, Liao KK. Valproate-induced encephalopathy. Zhonghua Yi Xue Za Zhi (Taipei) 2001; 64: 474-8. PubMed PMID: 1172014.

Lott RS, Helmboldt KM, Madaras-Kelly KJ. Retrospective evaluation of the effect of valproate therapy on transaminase elevations in patients with hepatitis C. Pharmacotherapy 2001; 21: 1345-51. PubMed PMID: 11714207.

(Serial ALT levels in 214 HCV positive patients, 28 on valproate, found no correlation with valproate use).

Barrueto F Jr, Hack JB. Hyperammonemia and coma without hepatic dysfunction induced by valproate therapy. Acad Emerg Med 2001; 8: 999-1001. PubMed PMID: 11581089.

(41 year old man developed altered mental status while on chronic valproate therapy [3 years], with ammonia of 377 μM but normal liver tests and normal valproate levels).

Bohan TP, Helton E, McDonald I, König SA, Gazitt S, Sugimoto T, Scheffner D, et al. Effect of L-carnitine treatment for valproate-induced hepatotoxicity. Neurology 2001; 56: 1405-9. PubMed PMID: 11376200.

(Analysis of 123 patients with valproate hepatotoxicity in international registry demonstrating marked improvement in survival with use of carnitine; there was 100% survival if iv carnitine was started within 5 days of symptomatic onset, compared to >80% fatality rate before introduction of carnitine).

DeVivo DC. Effect of L-carnitine treatment for valproate-induced hepatotoxicity. Neurology 2002; 58: 507-8. PubMed PMID: 11839873.

(Letter in response to Bohan et al. suggesting routine oral carnitine supplementation in patients on valproate).

Clarkson A, Choonara I. Surveillance for fatal suspected adverse drug reactions in the UK. Arch Dis Child. 2002; 87: 462-6. PubMed PMID: 12456539.

(Between 1964 and 2002 in the UK, there were 331 reported deaths in children due to medications, including 50 due to liver failure, 21 of which were attributed to valproate).

Longin E, Teich M, Koelfen W, König S. Topiramate enhances the risk of valproate-associated side effects in three children. Epilepsia 2002; 43: 451-4. PubMed PMID: 11952778.

(3 children, ages 1-9 years on valproate for few months to 5 years developed apathy and hypothermia 4-8 weeks after adding topiramate with ammonia elevations [one with ALT elevation as well], rapidly reversed by stopping either agent, positive rechallenge in one; topiramate appears to enhance risk of hyperammonemia due to valproate).

Vossler DG, Wilensky AJ, Cawthon DF, Abson Kraemer DL, Ojemann LM, Caylor LM, Morgan JD. Serum and CSF glutamine levels in valproate-related hyperammonemic encephalopathy. Epilepsia 2002; 43: 154-9. PubMed PMID: 11903461.

(In assessing 7 patients with hyperammonemia on valproate, elevations in glutamine found in CSF; serum valproate levels were usually normal).

Huang Y-L, Hong H-S, Wang Z-W, Kuo T-T. Fatal sodium valproate-induced hypersensitivity syndrome with lichenoid dermatitis and fulminant hepatitis. J Am Acad Dermatol 2003; 49: 416-9. PubMed PMID: 12894087.

(2 year old girl treated with valproate for myoclonic jerks developed fever and rash after 17 days followed by jaundice [bilirubin 37.8 mg/dL, ALT 3037 U/L, protime 50.2 sec], progressing to acute liver failure and death; biopsy showing microvesicular steatosis and necrosis).

Romero-Falcón A, de la Santa-Belda E, Garci;a-Contreras R, Varela JM. A case of valproate-associated hepatotoxicity treated with L-carnitine. Eur J Intern Med 2003; 14: 338-40. PubMed PMID: 13678762.

(16 year old male developed lethargy and jaundice 6 weeks after starting valproate for epilepsy [bilirubin 21 mg/dL, AST 3887 U/L, Alk P 406 U/L, normal valproate levels], given carnitine and recovered in ~3 weeks).

Ee LC, Shepherd RW, Cleghorn GJ, Lewindon PJ, Fawcett J, Strong RW, Lynch SV. Acute liver failure in children: A regional experience. J Paediatr Child Health 2003; 39: 107-10. PubMed PMID: 12603798.

(Among 26 children with acute liver failure referred to the Queensland Transplant Service between 1984 and 2000; 2 were transplanted for valproate liver injury, both of whom subsequently died of neurological disease despite good graft function).

Arévalo-Lorido JC, Carretero-Gómez J, Bureo-Dacal JC, Montero-Leal C, Bureo-Dacal P. Antiepileptic drug hypersensitivity syndrome in a patient treated with valproate. Br J Clin Pharmacol 2003; 55: 415-6. PubMed PMID: 12680893.

(36 year old man developed fever, rash, eosinophilia and lymphadenopathy 1 month after starting carbamazepine, improving with corticosteroid therapy, but recurring when valproate was started 2 weeks later).

Bumb A, Diederich N, Beyenburg S. Adding topiramate to valproate therapy may cause reversible hepatic failure. Epileptic Disord 2003; 5: 157-9. PubMed PMID: 14684351.

(51 year old woman with resistant epilepsy had topiramate added to valproate and developed confusion and liver injury [bilirubin not given, ALT 464 U/L, GGT 569 U/L, ammonia 88 µg/dL], improved on withdrawal of valproate; hypothesized that topiramate changed pharmacokinetics of valproate).

Nakazato Y, Ando S, Yamamoto T, Tamura N, Shimazu K. [Valproate-induced hyperammonemic encephalopathy in a patient with Sjögren's syndrome] Rinsho Shinkeigaku 2004; 44: 682-5. Japanese. PubMed PMID: 1556848.

McCall M, Bourgeois JA. Valproic acid-induced hyperammonemia: a case report. J Clin Psychopharmacol 2004; 24: 521-6. PubMed PMID: 15349008.

(62 year old woman on long term valproate developed dizziness, fatigue and confusion with normal valproate levels but 3 fold elevation in ammonia, minimal AST elevation, improvement with stopping; unclear what triggered the event).

Yehya N, Saldarini CT, Koski ME, Davanzo P. Valproate-induced hyperammonemic encephalopathy. J Am Acad Child Adolesc Psychiatry 2004; 43: 926-7. PubMed PMID: 15266186.

(9 year old boy with severe behavioral problems developed recurrent episodes of confusion and aggression on valproate with elevated ammonia levels improving with stopping valproate, liver tests normal).

Luef GJ, Waldmann M, Sturm W, Naser A, Trinka E, Unterberger I, Bauer G, et al. Valproate therapy and nonalcoholic fatty liver disease. Ann Neurol 2004; 55: 729-32. PubMed PMID: 15122714.

(Among 45 patients with epilepsy, ultrasound showed fatty liver in 63% of patients on valproate but only 23% on carbamazepine; ALT and AST similar, insulin resistance and overweight were more common with valproate treatment).

Lokrantz CM, Eriksson B, Rosén I, Asztely F. Hyperammonemic encephalopathy induced by a combination of valproate and pivmecillinam. Acta Neurol Scand 2004; 109: 297-301. PubMed PMID: 15016014.

(72 year old woman on valproate for 8 months developed stupor and coma 2 weeks after starting pivmecillinam for urinary tract infection [liver tests normal, ammonia 113 μM], pivmecillinam known to decrease carnitine levels).

Weng TI, Shih FF, Chen WJ. Unusual causes of hyperammonemia in the ED. Am J Emerg Med 2004; 22: 105-7. PubMed PMID: 15011224.

(Four case reports demonstrating various causes of hyperammonemia without liver disease; partial ornithine carbamoyltransferase deficiency, anticancer chemotherapy and valproate).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl 2004; 10: 1018-23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants done in the United States between 1990 and 2002, 137 [0.2%] were done for idiosyncratic drug induced acute liver failure, of which 10 were attributed to phenytoin, 10 to valproate and 1 to carbamazepine, but none to ethosuximide or other anticonvulsants).

Roepke S, Treudler R, Anghelescu I, Orfanos CE, Tebbe B. Valproic Acid and hypersensitivity syndrome. Am J Psychiatry 2004; 161: 579. PubMed PMID: 14992991.

(48 year old man developed fever, rash and lymphadenopathy 3 weeks after starting valproate with eosinophilia [24%] and slight elevations in "levels of transaminases", resolving with corticosteroid therapy).

Rahman M, Haider N. Anticonvulsant hypersensitivity syndrome from addition of lamotrigine to divalproex. Am J Psychiatry 2005; 162: 1021. PubMed PMID: 15863816.

(50 year old woman with bipolar disorder on valproate developed fever, rash and eosinophilia [5%] 2-3 weeks after starting lamotrigine [bilirubin and Alk P normal, ALT 186 U/L], resolving soon after stopping both valproate and lamotrigine).

Björnsson E, Jerlstad P, Bergqvist A, Olsson R. Fulminant drug-induced hepatic failure leading to death or liver transplantation in Sweden. Scand J Gastroenterol 2005; 40: 1095-101. PubMed PMID: 16165719.

(36 years of reporting to Swedish registry identified 103 cases of acute liver failure due to drugs; valproate listed as causing only one case).

Lheureux PE, Penaloza A, Zahir S, Gris M. Science review: carnitine in the treatment of valproic acid-induced toxicity–what is the evidence? Crit Care 2005; 9: 431-40. PubMed PMID: 16277730.

(Review of literature on efficacy of carnitine in reversing toxicity of valproate overdose, acute liver injury and hyperammonemia; efficacy largely based on use of historical controls).

Ortiz-Sáenz de Santa María R, Santiago-Fernández C, Cano-Del Pozo M, et al. [Treatment with valproate and hepatic steatosis] Rev Neurol 2005; 41: 766-7. PubMed PMID: 1635536.

Cuturic M, Abramson RK. Acute hyperammonemic coma with chronic valproic acid therapy. Ann Pharmacother 2005; 39: 2119-23. PubMed PMID: 16288075.

(56 year old woman on long term valproate for epilepsy developed episodic confusion after minor increase in valproate dose and stopping other agents; valproate dose increased and patient worsened and found to have high ammonia with normal liver tests).

Sato K, Ueda Y, Ueno K, Okamoto K, Iizuka H, Katsuda S. Hepatocellular carcinoma and nonalcoholic steatohepatitis developing during long-term administration of valproic acid. Virchows Arch 2005; 447: 996-9. PubMed PMID: 16133366.

(64 year old man treated with valproate for 17 years developed hepatocellular carcinoma with steatosis, Mallory bodies and bridging fibrosis, possibly related to nonalcoholic steatohepatitis).

Rath A, Naryanan TJ, Chowdhary GV, Murthy JM. Valproate-induced hyperammonemic encephalopathy with normal liver function. Neurol India 2005; 53: 226-8. PubMed PMID: 16010067.

(Review of 5 cases of hyperammonemia on valproate; 3 monotherapy, onset after 4-90 days with decreased sensorium, episodic vomiting, all had normal ALT, resolved with stopping without use of carnitine).

Bauer MS. Fatal hepatic failure and valproate. Am J Psychiatry 2005; 162: 192. PubMed PMID: 15625224.

(51 year old man with bipolar disorder developed jaundice 3 months after starting valproate with previously normal liver tests [bilirubin 9.1 mg/dL, ALT 3208 U/L, Alk P 172 U/L, protime 18.8 sec], died awaiting liver transplantation).

Kimmel RJ, Irwin SA, Meyer JM. Valproic acid-associated hyperammonemic encephalopathy: a case report from the psychiatric setting. Int Clin Psychopharmacol 2005; 20: 57-8. PubMed PMID: 15602119.

(50 year old woman on long term valproate for psychiatric reasons developed confusion and coma with high ammonia levels 4 months after adding lamotrigine, responding to stopping therapy).

König SA, Buesing D, Longin E, Oehring R, Haussermann P, Kluger G, Lindmayer F, et al. Valproic acid-induced hepatopathy: nine new fatalities in Germany from 1994 to 2003. Epilepsia 2006; 47: 2027-31. PubMed PMID: 17201699.

(Survey of all German members of International League Against Epilepsy identified 31 cases of valproate liver injury between 1994 and 2003; 9 fatal and 22 recovered cases; latency of 1-6 months, ALT 113-2160 U/L).

Kakinuma H, Fujiki T, Nakamura T, Takahashi H. Valproate hepatotoxicity in a 5-year-old boy with cerebral palsy due to neonatal asphyxia. Pediatr Int 2006; 48: 631-3. PubMed PMID: 17168987.

(5 year old boy with cerebral palsy had fever and status epilepticus and was treated with valproate, developing acute liver failure within a few days [bilirubin initially 1.0 mg/dL, ALT 8290 U/L, NH3 112 µg/mL], slow recovery and neurological residual; no metabolic abnormality found).

Björnsson E, Olsson R. Suspected drug-induced liver fatalities reported to the WHO database. Dig Liver Dis 2006; 38: 33-8. PubMed PMID: 16054882.

(In WHO database of fatal adverse drug reactions from 1968-2003 there were 4690 reports of drug induced liver fatality: valproate was the third most common cause [~130 cases]).

Tzoulis C, Engelsen BA, Telstad W, Aasly J, Zeviani M, Winterthun S, Ferrari G, Aarseth JH, Bindoff LA. The spectrum of clinical disease caused by the A467T and W748S POLG mutations: a study of 26 cases. Brain 2006; 129: 1685-92. PubMed PMID: 16638794.

(Clinical features of patients with A467T and/or W748S variants in DNA polymerase gamma; onset of epilepsy, headache, ataxia or speech delay usually in the teen years with relentless course of myoclonus and ataxia, 2 died of liver failure, but 7 developed acute liver failure after valproate therapy of seizures).

Horvath R, Hudson G, Ferrari G, Futterer N, Ahola S, Lamantea E, Prokisch H, et al. Phenotypic spectrum associated with mutations of the mitochondrial polymerase gamma gene. Brain 2006; 129: 1674-84. PubMed PMID: 16621917.

(Analysis of "large number" of patients with suspected mitochondrial disease [Alpers, familial progressive external ophthalmoplegia, late onset ataxia] for the mitochondrial DNA polymerase gamma sequence; identified frequent but heterogenous variants, A467T being common with encephalopathy and liver disease [often triggered by valproate], but found in other syndromes).

Alqahtani S, Federico P, Myers RP. A case of valproate-induced hyperammonemic encephalopathy: look beyond the liver. CMAJ 2007; 177: 568-9. PubMed PMID: 17846437.

(18 year old woman developed stupor and asterixis 2 weeks after starting valproate, with high ammonia levels and normal liver tests, and recovery within a week after stopping).

Wadzinski J, Franks R, Roane D, Bayard M. Valproate-associated hyperammonemic encephalopathy. J Am Board Fam Med 2007; 20: 499-502. PubMed PMID: 17823470.

(2 women, ages 29 and 51, developed hyperammonemia with confusion after 7 days and 5 months of high doses of valproate [normal bilirubin and ALT], with rapid improvement on stopping).

Velioğlu SK, Gazioğlu S. Non-convulsive status epilepticus secondary to valproic acid-induced hyperammonemic encephalopathy. Acta Neurol Scand 2007; 116: 128-32. PubMed PMID: 17661800.

(19 year old male developed stupor, coma and seizures 4 days after starting valproate, found to have high ammonia levels with normal ALT, bilirubin and valproate levels, resolving with stopping).

Carr RB, Shrewsbury K. Hyperammonemia due to valproic acid in the psychiatric setting. Am J Psychiatry 2007; 164: 1020-7. PubMed PMID: 17606652.

(45 year old woman treated with valproate for psychiatric disorder developed confusion after 6 days, later found with high ammonia levels despite normal ALT levels, improvement with stopping).

Attilakos A, Voudris KA, Katsarou E, Prassouli A, Mastroyianni S, Garoufi A. Transient decrease in serum albumin concentrations in epileptic children treated with sodium valproate monotherapy. Clin Neuropharmacol 2007; 30: 145-9. PubMed PMID: 17545749.

(26 children given valproate were monitored with liver tests at 0, 6, 12 and 24 months: only 1 had abnormal ALT [44 U/L], GGT normal in all, minimal overall increase in ALT and AST and decrease in albumin levels).

Tang W. Drug metabolite profiling and elucidation of drug-induced hepatotoxicity. Expert Opin Drug Metab Toxicol 2007; 3: 407-20. PubMed PMID: 17539747.

(Review of role of drug metabolic studies in elucidating cause of hepatotoxicity).

Chicharro AV, de Marinis AJ, Kanner AM. The measurement of ammonia blood levels in patients taking valproic acid: looking for problems where they do not exist? Epilepsy Behav 2007; 11: 361-6. PubMed PMID: 17845866.

(Review of literature on ammonia levels in patients on valproate, consistent finding of levels increasing 2 fold, but usually without symptoms and not requiring dose modification).

Russell S. Carnitine as an antidote for acute valproate toxicity in children. Curr Opinion Pediatr 2007; 19: 206-10. PubMed PMID: 17496767.

(Short review of valproate toxicity and clinical use of carnitine).

Gerstner T, Bauer MO, Longin E, Bell N, Koenig SA. Reversible hepatotoxicity, pancreatitis, coagulation disorder and simultaneous bone marrow suppression with valproate in a 2-year-old girl. Seizure 2007; 16: 554-6. PubMed PMID: 17493839.

(2 year old girl on valproate for over a year had severe liver injury [bilirubin not given, ALT 2510 U/L, lipase 725 U/L, normal valproate and ammonia levels], resolving upon stopping).

Chou HF, Yang RC, Chen CY, Jong YJ. Valproate-induced hyperammonemic encephalopathy. Pediatr neonatol 2008; 49: 201-4. PubMed PMID: 19133574.

(Adolescent developed dizziness within days of starting valproate, with normal ALT but ammonia five fold elevated, rapid recovery with stopping).

Tsai M-F, Chen C-Y. Valproate-induced hyperammonemic encephalopathy treated by hemodialysis. Ren Fail 2008; 30: 822-4. PubMed PMID: 18791959.

(14 year old girl developed dizziness within days of restarting higher doses of valproate with high ammonia and valproate levels, but normal ALT and bilirubin; the syndrome reversed within 12 hours with hemodialysis).

Nicolai J, Gunning B, Leroy PL, Ceulemans B, Vles JS. Acute hepatic injury in four children with Dravet syndrome: valproic acid, topiramate or acetaminophen? Seizure 2008; 17: 92-7. PubMed PMID: 17697789.

(4 children with severe infantile myoclonic epilepsy on chronic therapy with topiramate and valproate had sudden and transient onset of marked elevations in ALT [2229, 5898, 280 and 480 U/L] and hyperammonemia or coagulopathy without jaundice shortly after febrile illness and/or use of acetaminophen; possibly Reye syndrome due to valproate and topiramate, rapid recovery despite continuing anticonvulsants).

Dewan P, Aggarwal A, Faridi MM. Effect of phenytoin and valproic acid therapy on serum lipid levels and liver function tests. Indian Pediatr 2008; 45:855-8. PubMed PMID: 18948659.

(Cross sectional analysis of lipid and liver test results in 52 children on phenytoin or valproate showing minimal differences between groups).

Subhash HS, Heddle RJ, Schultz DW, Ring J, Thompson CH. Hepatic encephalopathy precipitated by sodium valproate therapy. Med J Aust 2008; 188: 549. PubMed PMID: 18459937.

(71 year old woman developed confusion 2 years after starting valproate with no change in liver tests; chronic Alk P elevations subsequently shown to be due to primary biliary cirrhosis).

McFarland R, Hudson G, Taylor RW, Green SH, Hodges S, McKiernan PJ, Chinnery PF, Ramesh V. Reversible valproate hepatotoxicity due to mutations in mitochondrial DNA polymerase gamma (POLG1). Arch Dis Child 2008; 93: 151-3. PubMed PMID: 18208989.

(2 year old boy developed stupor 2 months after starting valproate [bilirubin 0.6 rising to 6.4 mg/dL, ALT 249 U/L], who subsequently developed liver failure but recovered; gene sequencing showed several mutations in DNA polymerase gamma).

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

(Review of hepatotoxicity of all anticonvulsants; elevations in ALT or Alk P in up to 44% of users of valproate but serious toxicity occurs in only ~1:15,000 patients, higher in young children; 4 types of injury; asymptomatic enzyme elevations, acute hepatotoxicity, Reye syndrome and hyperammonemia).

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 cases, lamotrigine 5, phenytoin 5, gabapentin and topiramate 1 each).

Neyns B, Hoorens A, Stupp R. Valproic acid related idiosyncratic drug induced hepatotoxicity in a glioblastoma patient treated with temozolomide. Acta Neurol Belg 2008; 108: 131-4. PubMed PMID: 19239041.

(48 year old patient developed cholestatic hepatitis during therapy with temozolomide, cilengitide and valproate, which improved when all drugs were stopped and did not recur with restarting temozolomide).

Mata Zubillaga D, Prieto Espuñes S, Ferrero de la Mano L, Herrero Mendoza B. [Valproic acid induced-idiosyncratic hepatotoxicity]. An Pediatr (Barc) 2008; 69: 492-3. Spanish. PubMed PMID: 19128756.

(7 year old girl developed liver injury on valproate [peak bilirubin 9.5 mg/dL, ALT 2050 U/L, Alk P normal], resolving within a few weeks of stopping).

Verrotti A, Di Marco G, la Torre R, Pelliccia P, Chiarelli F. Nonalcoholic fatty liver disease during valproate therapy. Eur J Pediatr 2009; 168: 1391-4. PubMed PMID: 19184102.

(11 year old girl developed nonalcoholic fatty liver disease after 19 kg weight gain attributed to valproate, ALT levels rising from 30 to 80 U/L and returning to normal with weight loss after stopping valproate).

Franciotta D, Kwan P, Perucca E. Genetic basis for idiosyncratic reactions to antiepileptic drugs. Curr Opin Neurol 2009; 22: 144-9. PubMed PMID: 19262378.

*(Review of the genetic associations with hypersensitivity reactions to anticonvulsant medications; closest association has been with HLA-B*1502 and Stevens-Johnson syndrome after aromatic anticonvulsants).*

Lheureux PE, Hantson P. Carnitine in the treatment of valproic acid-induced toxicity. Clin Toxicol (Phila) 2009; 47: 101-11. (Review of the mechanism of action of carnitine in valproate hepatotoxicity and the clinical evidence of its efficacy, PubMed PMID: 19280426.

concludes that intravenous carnitidine "does not appear to be harmful and could be beneficial").

Waring WS, Nixon AC. Acute liver impairment after sodium valproate overdose. BMJ Case Rep 2009; 2009. pii: bcr06.2008.0057. PubMed PMID: 21686945.

(36 year old woman took an overdose of valproate [32 g] and developed nausea 36 hours later [bilirubin 1.5 mg/dL, ALT 761 U/L], symptoms resolving in 4 days and liver enzymes by 6 weeks).

Stewart JD, Horvath R, Baruffini E, Ferrero I, Bulst S, Watkins PB, Fontana RJ, Day CP, Chinnery PF. Polymerase γ gene POLG determines the risk of sodium valproate-induced liver toxicity. Hepatology 2010; 52: 1791-6. (Among PubMed PMID: 21038416.

17 US patients identified with valproate hepatotoxicity, 8 had genetic variations in the mitochondrial DNA polymerase gamma gene, a rate more than 20-fold higher than population controls).

Nishri D, Blumkin L, Lev D, Leshinsky-Silver E, Abu-Rashid M, Birch R, Zuberi SM, Lerman-Sagie T. Hepatic coma culminating in severe brain damage in a child with a SCN1A mutation. Eur J Paediatr Neurol 2010; 14: 456-9. PubMed PMID: 20392657.

(11 month old boy developed status epilepticus and "fulminant liver failure" 2 months after starting valproate for myoclonic epilepsy [bilirubin not given, ALT peak 20,657 U/L, ammonia 380 micromol/L], with brain edema and residual neurologic defects, the mitochondrial DNA polymerase gamma gene was normal but variation found in the alpha-1 subunit gene of the voltage-gated neuronal sodium channel [SCN1A]).

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 [11%] were attributed to drug induced liver injury of which 11 were due to antiepileptic drugs, 2 due to valproate).

Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol 2010; 105: 2396-404. PubMed PMID: 20648003.

(313 cases of drug induced liver injury were seen over a 12 year period at a large hospital in Bangalore, India; 3 [1.0%] were attributed to valproate, none of which were fatal).

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.

(Worldwide pharmacovigilance database contained 9036 hepatic adverse drug reactions in children, valproate accounting for 208 cases [2.3%: ranking third] for an adjusted risk odds ratio of 4.0).

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).

Rupasinghe J, Jasinarachchi M. Progressive encephalopathy with cerebral oedema and infarctions associated with valproate and diazepam overdose. J Clin Neurosci 2011; 18: 710-1. PubMed PMID: 21349718.

(29 year old man developed stupor and coma within hours of taking an overdose of valproate [4 g] and diazepam [75 mg], with normal bilirubin and liver enzymes but high ammonia [348 micromol/L], and cerebral edema resulting in residual neurological defects).

Verrotti A, Agostinelli S, Parisi P, Chiarelli F, Coppola G. Nonalcoholic fatty liver disease in adolescents receiving valproic acid. Epilepsy Behav 2011; 20: 382-5. (Among PubMed PMID: 21256090.

86 adolescents on valproate, fatty liver was present in 36% by ultrasound and a similar proportion [34.5%] of 43 weight-matched controls).

Chaudrey KH, Naser TB, Steinberg A, Avashia KD, Nouri-Kolouri M, Asadi S, Irshad Khan SI, Ihsan M. Thinking Beyond the Obvious: Hepatotoxicity Secondary to Idiosyncratic Depakote Toxicity. Am J Ther 2011. [Epub ahead of print] PubMed PMID: 21248613.

(25 year old woman developed confusion while taking valproate and was found to have metabolic acidosis [bilirubin and Alk P not given, ALT 90 U/L, ammonia 143 µmol/L, valproate levels normal], resolving rapidly upon stopping).

Mindikoglu AL, King D, Magder LS, Ozolek JA, Mazariegos GV, Shneider BL. Valproic acid-associated acute liver failure in children: case report and analysis of liver transplantation outcomes in the United States. J Pediatr 2011; 158: 802-7. PubMed PMID: 21167499.

(Among 98 children who underwent liver transplantation for drug induced liver injury in the United States between 1987 and 2009, 17 [17%] had valproate induced injury, 15 of whom were less than 8 years old and had poor posttransplant survival compared to controls transplanted for acute liver failure from other agents [20% vs 69% at 1 year]).

Tarafdar S, Slee M, Ameer F, Doogue M. A case of valproate induced hyperammonemic encephalopathy. Case Report Med 2011; 2011: 969505. PubMed PMID: 21629819.

(36 year old man on valproate developed confusion after an alcoholic binge [ammonia 248 µmol/L, valproate levels normal], resolving within 3 days of stopping).

Ghozzi H, Hakim A, Sahnoun Z, Ben Mahmoud L, Atheymen R, Hammami S, Zeghal K. [Relationship between plasma concentrations of valproic acid and hepatotoxicity in patients receiving high doses]. Rev Neurol (Paris) 2011; 167: 600-6. PubMed PMID: 21492891.

(In testing 425 patients, no association was found with side effects and plasma levels of valproate).

Pronicka E, Weglewska-Jurkiewicz A, Pronicki M, Sykut-Cegielska J, Kowalski P, Pajdowska M, Jankowska I, Kotulska K, Kalicinski P, Jakobkiewicz-Banecka J, Wegrzyn G. Drug-resistant epilepsia and fulminant

valproate liver toxicity. Alpers-Huttenlocher syndrome in two children confirmed post mortem by identification of p.W748S mutation in POLG gene. Med Sci Monit 2011; 17: CR203-9. PubMed PMID: 21455106.

(Retrospective analysis of 28 children with mitochondrial encephalopathy found p.W748S mutation in the polymerase gamma gene [typical of Alpers-Huttenlocher Syndrome] in two, both of whom died of liver failure a few months after starting valproate for seizures; liver tissue showed mitochondrial depletion).

Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, Roujeau JC. The DRESS syndrome: a literature review. Am J Med 2011; 124: 588-97. PubMed PMID: 21592453.

(Systematic review of literature on DRESS identified 172 cases due to 44 drugs, most frequently carbamazepine [27%], allopurinol [11%] and lamotrigine [6%]; no cases were linked to valproate).

Sedky K, Nazir R, Joshi A, Kaur G, Lippmann S. Which psychotropic medications induce hepatotoxicity? Gen Hosp Psychiatry 2012; 34: 53-61. Review. PubMed PMID: 22133982.

(Review of hepatotoxicity of psychotropic medications with summary of literature).

Hunter MF, Peters H, Salemi R, Thorburn D, Mackay MT. Alpers syndrome with mutations in POLG: clinical and investigative features. Pediatr Neurol 2011 ; 45: 311-8. PubMed PMID: 22000311.

(Clinical description of 12 children with Alpers syndrome who were homozygotes or compound heterozygotes for mutations in the polymerase gamma gene; all had developmental delay and seizures starting before 2 years of age and died by age 11, often with cirrhosis or acute liver failure particularly if treated with valproate).

Prins MC, van Meijel JJ. A case of hyperammonaemic encephalopathy due to valproic acid. Neth J Med 2011; 69: 389-91. (PubMed PMID: 21978982.

57 year old man developed progressive stupor while on chronic valproate therapy [liver tests normal, ammonia 132 µmol/L, valproate levels high], resolving rapidly upon stopping).

Bota RG, Ligasan AP, Najdowski TG, Novac A. Acute hypersensitivity syndrome caused by valproic Acid: a review of the literature and a case report. Perm J 2011; 15: 80-4. PubMed PMID: 21841930.

(25 year old woman with bipolar disorder developed fever within one week of starting valproate, followed by jaundice and rash [bilirubin 10.2 mg/dL, ALT 767 U/L, Alk P 681 U/L], treated with corticosteroids and resolving within a month of stopping).

Holroyd S, Overdyke JT. Hyperammonemia associated with valproic Acid use in elderly psychiatric patients. J Neuropsychiatry Clin Neurosci 2012; 24: 372-4. PubMed PMID: 23037652.

(Retrospective analysis of 12 elderly subjects treated with valproate for 1 to 60 months; liver tests were normal, but 10 [83%] had elevated ammonia levels and 3 had history of confusion or delirium).

Schmid MM, Freudenmann RW, Keller F, Connemann BJ, Hiemke C, Gahr M, Kratzer W, Fuchs M, Schönfeldt-Lecuona C. Non-Fatal and Fatal Liver Failure Associated with Valproic Acid. Pharmacopsychiatry 2012 Aug 22. PubMed PMID: 22915484.

(Between 1993 and 2009, 132 cases of severe valproate hepatotoxicity were reported to the German Federal regulatory agency, of which 34 [25%] were fatal).

Chatzistefanidis D, Georgiou I, Kyritsis AP, Markoula S. Functional impact and prevalence of polymorphisms involved in the hepatic glucuronidation of valproic acid. Pharmacogenomics 2012; 13: 1055-71. PubMed PMID: 22838952.

(Review of the metabolism of valproate which is mainly via glucuronidation mediated by UDP glucuronsyltransferases [UGTs] in the liver).

van Zoelen MA, de Graaf M, van Dijk MR, Bogte A, van Erpecum KJ, Rockmann H, Maarschalk-Ellerbroek LJ. Valproic acid-induced DRESS syndrome with acute liver failure. Neth J Med 2012; 70: 155. PubMed PMID: 22516584.

(26 year old man developed fever, rash, lymphadenopathy, facial edema and jaundice 6 weeks after starting valproate [bilirubin 10.9 mg/dL, ALT 2800 U/L, Alk P 456 U/L, protime 21.6 sec], eventually resolving after stopping and with corticosteroid therapy: Case 3).

Lin YH, Chien YL. Valproic Acid-related anticonvulsant hypersensitivity syndrome and subsequent olanzapine-related neutropenia and thrombocytopenia: a case report. J Clin Psychopharmaco 2012; 32: 132-3. (27 year old woman developed fever and rash 12 days after starting valproate [bilirubin and Alk P not given; ALT 107 U/L], resolving rapidly upon stopping and with prednisolone therapy, later developing neutropenia on olanzapine). PubMed PMID: 22217947.

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, 2 of which were attributed to phenytoin, but none were linked to valproate use).

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

(Concise review of drugs of choice for epilepsy; valproate is effective in several forms of seizures and is also used to treat migraine headaches and bipolar disorder; serious adverse effects are uncommon, but fatal liver failure has been reported particularly in children but also in adults).