Common and uncommon adverse effects of AEDs in children

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Adverse effects (AE)

	Dose-related AE	Idiosyncretic AE
Onset	After increasing dose	First few weeks of therapy
Relationship with dose	Common with increasing dose	Uncommon
Mechanism	Known pharmacological action of AED	Cytotoxic or immunologic effect triggered by AED
Treatment	Dose adjustment	Discontinuation of AED
Prevention	Optimize dose carefully	Avoid specific AED in high risk group

Zaccara et al. Epilepsia 2007

Dose-related adverse effect (AE)

Risk factors

- Liver disease: LTG
- Renal disease: TPM, GBP
- Ketogenic diet: TPM, ZNS
- Starting dose, titration rate
- Multiple AEDs

Guerrini et al. Drug Saf 2012
Sarco and Bourgeois, CNS Drugs 2010

Common dose-related AE

AED	somnolence	dizziness	tremor	ataxia	diplopia	n/v	anorexia	Wt. gain
PB	+	+	+	+	+			
PHT		+	+	+	+	+		
CBZ	+	+	+	+	+	+		
VPA			+	+		+		+
TPM	+	+		+		+	+	
LEV	+					+	+	
LTG	+	+	+	+	+	+		
OXC	+	+		+	+	+		
VGB	+					+		+
ZNS	+	+		+		+	+	
GBP	+	+		+		+		
PGB	+	+						+

Specific dose-related AE

AE	AEDs
Insomnia	PB, LTG
Tremor	VPA
Arrhythmia	CBZ, PHT
Leukopenia	CBZ, PHT
Macrocytic anemia (folate)	CBZ, PHT, PB
Thrombocytopenia	VPA
Hyponatremia	OXC, CBZ
Metabolic acidosis, oligohydrosis	TPM, ZNS

Toledano, Gil-Nagel. Semin Neurol 2008

VPA: Thrombocytopenia

- Platelet is usually not lower than 50,000
- High incidence at high serum concentration
- Seldom lead to drug discontinuation
- Improve with dosage reduction

May, Sunder. Epilepsia 1993
Beydoun et al. Neurology 1997

VPA: hyperammonemic encephalopathy

- Case reports, mostly within 4 months (up to 2 yr)
- Drowsiness → coma, vomiting, seizure
- Probably dose-related, high therapeutic level
- Mechanism: accumulation of toxic metabolite
- However, poor predictor with VPA level, dose, ammonia level and encephalopathy
- L-carnitine improves symptoms

Nanau, Neuman. Clin Biochem 2013

CBZ: Leukopenia

Transient leukopenia (10-20%)

- Occurred within first 3 months after treatment

Gilhus, Matre. Acta Neurol Scand 1986

Persistent leukopenia (2%)

- Reversible after discontinuation

Hart, Easton. Ann Neurol 1982

Hyponatremia

CBZ (high dose) – uncommon in children

Lahr. Clin Pharmacol Ther 1985

OXC

- Symptomatic hyponatremia (1.3%)
- Serum sodium < 125 mmol/L (2.6%)
- Mechanism: direct effect on collecting tubules or enhancement of ADH responsiveness

Holtmann et al. Neuropediatrics 2002
Van Amelsvoort et al. Epilepsia 1994

Phenytoin

- Long-term treatment
- Gingival hyperplasia, hirsutism, acne (13-40%)
- Improve after discontinuation

Dahllof et al. Epilepsia 1993

- Cerebellar atrophy: long-term use or acute use of high dose

Lindvall, Nilsson. Ann Neurol 1984

Cognitive effect

Cognitive impairment

- Phenobarbital: memory, attention, lower IQ (8.4 points) may improve after discontinuation (5 points lower)

Farwell et al. NEJM 1990 Chen et al. Epilepsy Res 2001

- Topiramate: language/speech (2-16%) – more in adult attention, memory, cognitive dullness (4-31%) - reduce with slow titration

Pandina et al. Pediatr Neurol 2010
Reith et al. J Paediatr Child Health 2003

Probable impairment: PHT (high dose, polytherapy)
CBZ (high dose), ZNS (2-19%)

Dominique, aldenkamp. Handbook of Clinical Neurology 2013
Sarco and Bourgeois, CNS Drugs 2010

Cognitive effect

Cognitive improvement

- Lamotrigine: attention

Brodbeck et al. Eur J Paediatr Neuro 2006

Probable improvement

- Oxcarbazepine: attention

No effect: LEV, VPA (except hyperammonemia)
No available data: VBG, GBP

Dominique, aldenkamp. Handbook of Clinical Neurology 2013

Topiramate

Metabolic acidosis (11-15%)

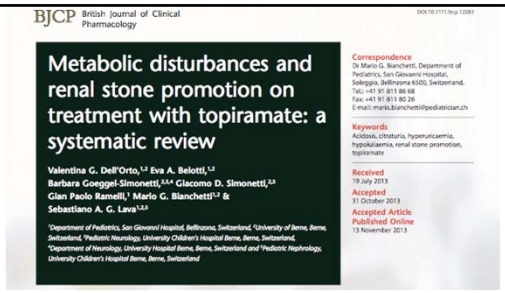
- Higher risk in young children and dosage > 6 mg/kg/day
- Usually asymptomatic

Ziad et al. Neurology 2005
Philippi et al. Epilepsia 2002

Renal stone (1.1-1.5%) due to carbonic anhydrase inhibition effect

- Lower risk in children (0.3-0.5%)

Wasserstein et al. Epilepsia 1995
Mikaeloff et al. Epilepsy Res 2003


BJCP British Journal of Clinical Pharmacology

Metabolic disturbances and renal stone promotion on treatment with topiramate: a systematic review

Valentina G. Dell'Orto, Eva A. Belotti, Barbara Goeggel-Simonetti, Giacomo D. Simonetti, Gian Paolo Ramelli, Mario G. Bianchetti & Sebastiano A. G. Lava

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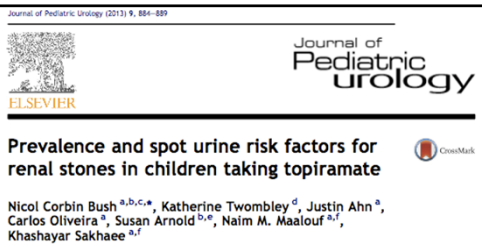
- Metabolic acidosis: no correlation with dosage
- Mild hypokalemia, mild hyperuricemia (adult)
- Hypocitraturia: 100% in patient with renal stone


Journal of Pediatric Urology (2013) 9, 884–889

Journal of Pediatric urology

ELSEVIER

Prevalence and spot urine risk factors for renal stones in children taking topiramate

Nicol Corbin Bush, Katherine Twombley, Justin Ahn, Carlos Oliveira, Susan Arnold, Naim M. Maalouf, Khashayar Sakhaee

- 41 high risk children, mean dosage 8 MKD, mean duration 27 months (1-112)
- 4.9% had renal stones (duration 4, 50 mos)
- Risk factors: hypocitraturia, hypercalciuria, high urine pH

Topiramate

- Oligohydrosis and hyperthermia (5-26%)
- More common in hot climate
- Reversible, mild, asymptomatic
- More common in children
- Due to carbonic anhydrase inhibition effect at sweat glands

Cerminara et al. Pediatr Neurol 2006
De Carolis et al. Epilepsia 2003

TPM: oligohydrosis

Ben-Zeev et al. J Child Neurol 2003

- 13 cases who had symptom of decreased sweating, 14 control cases
- 9/13 had reduced sweat quantity (5%) on pilocarpine sweat test compared to control
- 8/9 were children, age < 16 yrs
- Only 30% had symptoms of heat intolerance

Zonisamide

Oligohydrosis (3-25% in US) higher than in Japanese (1%), approx 13 per 10,000 exposure-yr

- More common in children, mildly symptomatic
- Reversible if discontinuation

Low et al. Epilepsy Res 2004
Knudsen et al. Pediatr Neurol 2003

Renal stone

- Rare, 0-4%, higher in US
- Mostly in adult

Kubota et al. Brain Dev 2000
Leppik et al. Epilepsy Res 2006

Gabapentin

Behavioral problem esp. in young children with mental retardation

- Incidence 3-8%
- Hyperactivity, impulsiveness, irritability
- Dose reduction can improve symptoms

Mikati et al. J Intellect Disabil Res 1998
Lee et al. Epilepsia 1996

Levetiracetam

- Somnolence 16.3% (10% in placebo)
- Infection 8.3% (3% in placebo)
- Only significance in adult, not in children

Mbizvo et al. 2014

Lamotrigine (LTG)

- Liver enzyme elevation (10%)
- Insomnia (6%)

Chung, Eiland. Pediatr Drugs 2008
Malphrus, Wilfong. Curr Treat Options Neurol 2007

Vigabatrin (VGB)

- Irritability / agitation (2-30%)

Idiosyncratic AE

Caused by

- Direct cytotoxicity of drug or its metabolite eg. VPA-induced hepatotoxicity
- Immune mediated reaction either humoral or cell-mediated responses eg. DRESS
- Off-target pharmacology eg. choreoathetoid reaction from PHT or other unusual CNS effects

Zaccara et al. Epilepsia 2007

Idiosyncratic AE

Risk factors

- Genetic predisposition: CBZ
- Young age: VPA
- Concomitant disease: VPA
- Associated drug: VPA-LTG
- Previous allergic drug reaction: aromatic AEDs
- Starting dose, titration rate: LTG

Guerrini et al. Drug Saf 2012

Idiosyncratic AE

1st generation AEDs	Severe idiosyncratic AE
Phenobarbital	SJS/TEN, DRESS, liver toxicity
Phynytoin	SJS/TEN, DRESS, liver toxicity, agranulocytosis
Sodium valproate	Liver toxicity, pancreatitis, (encephalopathy)
Carbamazepine	SJS/TEN, DRESS, aplastic anemia, agranulocytosis
Clonazepam	No
Clobazam	No
Nitrazepam	Drooling, aspiration

Zaccara et al. Epilepsia 2007

Risk of rash from AEDs

High risk	Moderate risk	Low risk
PHT (10%) CBZ (8.7%) LTG (6.2%)	PB OXC CLB ZNS	VPA TPM LEV GBP VGB

CBZ and OXC: cross reactivity 30%

Arif et al. Neurology 2007

Aromatic ring AED: cross reactivity 40-80%

Hyson, Sadler. 1997 Krauss. Epilepsy Curr 2006

LTG with VPA without adjusting dose in children < 13 yrs

Hirsch et al. Epilepsia 2006

SJS / TEN

- Annual incidence 0.4-1.2 cases per million
- 50% of SJS, 80% of TEN caused by drugs, AEDs is the most frequent esp. LTG, CBZ, PHT, PB
- Rare with VPA, GBP, OXC, TPM, ZNS
- 0ccurred within first 2 months of treatment
- CBZ and HLA B1502

Chang et al. 2006
Battino et al. 2000

DRESS

- Drug Reaction with Eosinophilia and Systemic Symptoms
- Anticonvulsant hypersensitivity syndrome (AHS)
- Rare, but more common than SJS
- Life threatening, mortality rate 10-20%
- Estimated incidence: 1 per 1,000 – 10,000 exposures
- Occurred 1 week – 3 months after treatment

Ganeva et al. Int J Dermatol 2008
Criado et al. An Bras Dermatol 2012
Knowles et al. Expert Opin Drug Saf 2012

DRESS

- PB, PHT, CBZ ('aromatic' anticonvulsants) – common
- PHT 2.3-4.5 cases per 10,000 exposures
- CBZ 1-4 cases per 10,000 exposures
- Cross reactivity 40-80%
- LTG, ZNS, OXC – also containing aromatic structure

Tennis, Stern Neurology 1997
Schlienger et al. Epilepsia 1998

DRESS

Clinical

- MP rash, erythroderma 80-100%
- Fever 60-100%
- Eosinophilia 58-100% (for PHT, CBZ, PB)

  LTG: more severe rash, less eosiniphilia (21%) and lymphadenopathy
- Liver abnormality > 60%
- Renal, lung, cardiac abnormality - rare

Schlienger et al. Neurology 1998
Peyriere et al. Therapeutics 2006

VPA: Liver toxicity/failure

- Potentially fatal
- First 3 months of treatment, very rare after 6 m
- Higher risk in
- Age < 2 years, polytherapy with enzyme inducing AED, inborn errors of metabolism, previous lever disease, mental retardation
- Risk ~ 1:600 (< 3 yr with polytherapy)

  ~ 1:16,000 (3-10 yr with monotherapy)

Bryant et al. Neurology 1996

Liver toxicity from other AEDs

- Aromatic AEDs (CAZ, PB, PHT) – immune mediated reaction with granulomatous infiltration in liver
- Usually occurred within 4 weeks
- Exact incidence – unknown
- May be associated with DRESS
- CBZ: estimated risk ~ 16 cases per 100,000 treatment years

Dreifuss, Langer. 1987
Askmark et al. 1990

VPA: pancreatitis - uncommon

- Rare, 1:40,000
- Mostly occurred within first year of treatment
- Higher risk in children, polytherapy, hemodialysis
- Abdominal pain and vomiting as initial symptom
- Normal serum amylase (25%)

Genton and Gelisse, antiepileptic drugs 2002
Asconape et al. Epilepsia 1993
Grauso-Eby et al. Pediatr Neurol 2003

Hematologic

Aplastic anemia - uncommon

- Felbamate: 127 cases per million (1:10,000)
- CBZ: 1:50,000 – 1:200,000
- Rare with LTG, PHT, ZNS

Pellock et al. Epilepsy Res 2006

Agranulocytosis - uncommon

- CBZ: increased risk with odds ratio 10.96
- Rare with PHT and very rare with PB, ZNS
- but mild leukopenia is dose-related

Ibanez et al. Arch Intern Med 2005

Drug-induced SLE

- CBZ
- PHT, VPA, PB, LTG: less frequent
- Absence of SLE symptoms before starting AED
- Remission within weeks after discontinuation
- No high titer of anti-dsDNA

Battino et al. 2000
Verma et al. Chest 2000

Idiosyncratic AE

2nd and 3rd gen AEDs	Severe idiosyncratic AE
Topiramate	Acute secondary angle-closure glaucoma
Levetiracetam	Psychotic event
Oxcarbazepine	SJS/TEN
Vigabatrin	Visual field defect
Lamotrigine	SJS/TEN, aplastic anemia
Gabapentin	Behavioral problem, hostility
Zonisamide	No
Pregabalin	No
Lacosamide	No

Zaccara et al. Epilepsia 2007

TPM: acute angle-closure glaucoma

- Very rare in children younger than 8 years, less than 5 cases reported
- 81 cases reported up to 2002, mostly adult
- Often bilateral
- Mostly occurred within 1 month, mean onset is 7 days after starting
- Blurred vision as presenting symptom
- Reversible immediately after discontinuation

Fraunfelder et al.Ophthalmology 2004
Al Ajlouni et al. Seizure 2005

Acute angle-closure glaucoma

- Associated with acute myopia
- Mechanism: ciliochoroidal effusion → ciliary body edema → iris bowing forward blocking drainage
- Caused by sulfonamide as idiosyncratic response
- Also found in other sulfonamide drug eg. Acetazolamide, HCTZ, sulfasalazine

Rapoport et al. BMC Pediatrics 2014

LEV: behavioral effect

- Emotional lability (1.7%), hostility (1.7%), anxiety (1.2%)

Morrell et al. epilepsy Res 2003

Mbizvo et al. (2014) review: RCT only, 300 children and 1,500 adult

- Overall, adult 1.7% (placebo 1%)

  children 40% (placebo 21%) - significant

Glauser et al. Neurology 2006
Levisohn et al. Epilepsia 2009

Vigabatrin: visual field defect

- Mostly permanent peripheral visual field defect
- Incidence: 13-34% (children)
- Higher risk if high dose, longer duration (> 6 months), male and age > 12 years
- Dose-related ? – unclear.
- No visual field defect even long-term exposure (> 10 yrs)

Vanhatalo et al. Neurology 1999
Iannetti et al. Pediatrics 2000
You et al. J Korean Med Sci 2006
Maguire et al. Epilepsia 2010

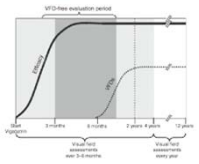
VGB recommendation

If VGB is effective

- Eye evaluation ± ERG, VEP at baseline and every 3 months is recommended

If VGB is not effective within 12 wks (CPS), 4 wks (IS)

- Discontinuation for minimizing visual field defect



Wheless et al. Neurotherapeutics 2007
Pellock. Acta Neurol Scand 2011

VGB recommendation

- If visual field defect developed → discontinue VGB
- The defect is not likely to progress to clinical significance after discontinuation
- Visual field evaluation is challenging in infant and young children
- Infantile spasm, VGB duration up to 6 months is appropriate for responsive case

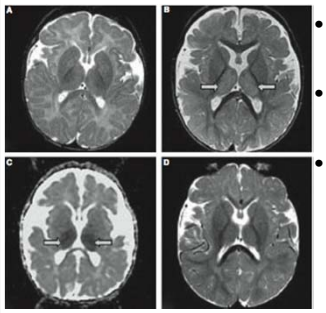
Sergott et al. Neuroophthalmology 2010
Carmant. Acta Neurol Scand 2011

Vigabatrin: MRI hyperintensity

- Infant and young children esp. < 2 years
- New, transient, reversible lesion
- Incidence: 22-34%
- Thalamus, globus pallidus, brainstem, corpus callosum

Pearl et al. Epilepsia 2009
Wheless et al. Epilepsia 2009

VGB: intramyelinic edema



- Increased T2 intensity and restricted diffusion
- Resolved after discontinuation
- Correlated with delayed evoked potential

Pearl et al. Epilepsia 2009
Walker, Kalviainen. Acta Neurol Scand 2011

AED-induced seizure aggravation

Epileptic syndrome / Sz	AEDs
BRE	CBZ, OXC, PB
JME	CBZ, OXC, PHT, LTG, GBP
SMEI	LTG, CBZ
PME	CBZ, PHT
CSWS / LKS	CBZ, LTG
LGS (tonic SE)	Benzodiazepine (iv)
Absence, myoclonic sz	CBZ, OXC, PHT, VGB, PGB

Chaves, Sander. Epilepsia 2005
Perucca et al. Epilepsia 1998
Guerrini et al. Epilepsia 1998
Genton. Brain Dev 2000
Corda et al. Epilepsia 2001