On-line resource:

Psychobehavioral and cognitive adverse events of anti-seizure medications for the treatment of developmental and epileptic encephalopathies

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Supplemental Table S1: Evidence of ASM-associated PBAEs

ASM Generation	Cochrane review of RCTs for adjunctive therapy in DRE: AEs significantly associated with ASM	Chen et al: observational study of PBAEs /discontinuations due to PBAEs		Steinhoff et al [1]: SLR of observational studies evaluating irritability, anger, or aggression with BRV, LEV, PER, and TPM in adults with epilepsy: weighted mean incidences/ discontinuation rates
		Adults with epilepsy (80% with DREs)* [2]	Children with epilepsy (80% with DREs)† [3]	
Valproate (VPA)	-	N=868 3.5%/0.9%	N=285 8.4%/3.2%	-
Clobazam (CLB)	Limited data: drowsiness most common [4]	N=645 4.5%/0.9%	N=89 2.3%/2.3%	-
Topiramate (TPM)	12 trials (1650 participants) identified. Ataxia 2.29 (99% CI 1.10 to 4.77; 4 studies); **concentration difficulties 7.81 (99% CI 2.08 to 29.29; 6 studies; moderate-certainty evidence**); dizziness 1.52 (99% CI 1.07 to 2.16; 8 studies); fatigue 2.08 (99% CI 1.37 to 3.15; 10 studies); paraesthesia 3.65 (99% CI 1.58 to 8.39; 7 studies; moderate-certainty evidence); **somnolence 2.44 (99% CI 1.61 to 3.68; 9 studies)**; **'thinking abnormally' 5.70 (99% CI 2.26 to 14.38; 4 studies; high-certainty evidence**); and weight loss 3.99 (99% CI 1.82 to 8.72; 9 studies; low-certainty evidence) [5]	N=639 6.3%/2.5%	N=212 6.1%/0.9%	Irritability: 3.1%/ 2.2% Anger: 0.2%/0% Aggression: 0.5%/1.2%
Cannabidiol (CBD) (+CLB for DS & LGS in the EU)	**-**	-	-	-
Fenfluramine (FFA)	**-**	-	-	-
Levetiracetam (LEV)	14 trials (2455 participants) identified. Overall: **somnolence: 13% (RR 1.62, 99% CI 1.19 to 2.20; P < 0.00001, I^2 = 0%; moderate-certainty evidence**); headache: affected 8% of participants (RR 0.85, 99% CI 0.59 to 1.21; P = 0.23, I^2 = 66%; low-certainty evidence); dizziness: affected 7% of participants (RR 1.54, 99% CI 0.98 to 2.41; P = 0.01, I^2 =15%; moderate-certainty evidence); fatigue (asthenia): affected 6% of participants (RR 1.53, 99% CI 0.98 to 2.38; P = 0.01, I^2 = 0%; moderate-certainty evidence); accidental injury: affected 6% of participants (pooled RR 0.72, 99% CI 0.49 to 1.06; P = 0.03, I^2 = 60%; low-certainty evidence). Combined behavioural AEs: 4.53% (RR 1.87, 99% CI 1.19 to 2.95; P = 0.0004).	N=1890 22.1%/8.3% Higher rates of irritability, depressive mood, anxiety, aggression, and other behavioral problems.	N=308 16.2%/6.8%	Irritability: 9.9%/ 3.4% Anger: 2.5%/0% Aggression: 2.6%/2.4%

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		Adults with epilepsy (80% with DREs)* [2]	Children with epilepsy (80% with DREs)† [3]	
	Children: **somnolence (RR 1.90, 99% CI 0.88 to 4.09; P = 0.03)**, vomiting (RR 1.22, 99% CI 0.55 to 2.69; P = 0.52), pharyngitis (RR 1.09, 99% CI 0.47 to 2.50; P = 0.79), **aggression (hostility) (RR 1.72, 99% CI 0.64 to 4.63; P = 0.16)**, and accidental injury (RR 1.63, 99% CI 0.63 to 4.26; P = 0.19). **Combined behavioural AEs in children: 22.64% (RR 1.90, 99% CI 1.16 to 3.11; P = 0.0009)** Combined behavioural AEs in adults: 1% (RR 1.79, 99% CI 0.59 to 5.41, P=0.17) **LEV was not significantly associated with an increased risk of any individual PBAEs alone, the most frequent being hostility, personality disorder, nervousness, depression, aggression, agitation, emotional lability, and psychomotor hyperactivity, each occurring in 1-0.5% of patients [6]**			
Brivaracetam (BRV)	6 trials (2411 participants) identified. Risk of individual AEs not reported [7]	-	-	Irritability: 5.6%/0.8% Anger: 3.3%/0% Aggression: 2.5%/0.8% Switching from LEV to BRV improved PBAEs in 33.3–83.0% of patients (weighted mean=66.6% across 5 observational studies, n=156)
Zonisamide (ZNS)	8 trials (1636 participants) identified. Ataxia (RR 3.85, 99% CI 1.36 to 10.93; 4 trials, 734 participants; low-certainty evidence); **somnolence (RR 1.52, 99% CI 1.00 to 2.31; 8 trials, 1636 participants; moderate-certainty evidence)**; **agitation (RR 2.35, 99% CI 1.05 to 5.27; 4 trials, 598 participants; low-certainty evidence)**; and anorexia (RR 2.74, 99% CI 1.64 to 4.60; 6 trials, 1181 participants; low-certainty evidence) [8]	N=760 9.7%/4.9% Higher rates of depressive mood	N=164 9.8%/6.7%	-
Perampanel (PER)	-	-	-	Irritability: 12.3%/ 3.0% Anger: 2.0%/0% Aggression: 4.4%/9.2%

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		Adults with epilepsy (80% with DREs)* [2]	Children with epilepsy (80% with DREs)† [3]	
Ethosuximide (ESM)	-	-	N=28 14.3%/7.1%	-
Stiripentol (STP) (+VPA+CLB)	One study identified: Neurological adverse effects (RR 2.65, 95% CI 0.88 to 8.01; gastrointestinal adverse effects (RR 11.56, 95% CI 0.71 to 189.36); CIs are wide [9]	-	-	-
Rufinamide (RUF)	6 trials (1759 participants) identified. Headache 1.36 (95% CI 1.08 to 1.69; 3 RCTs, 1228 participants; high-certainty evidence); dizziness 2.52 (95% CI 1.90 to 3.34; 3 RCTs, 1295 participants; moderate-certainty evidence); **somnolence 1.94 (95% CI 1.44 to 2.61; 6 RCTs, 1759 participants; moderate-certainty evidence)**; vomiting 2.95 (95% CI 1.80 to 4.82; 4 RCTs, 777 participants; low-certainty evidence); nausea 1.87 (95% CI 1.33 to 2.64; 3 RCTs, 1295 participants; moderate-certainty evidence); fatigue 1.46 (95% CI 1.08 to 1.97; 3 RCTs, 1295 participants; moderate-certainty evidence); and diplopia 4.60 (95% CI 2.53 to 8.38; 3 RCTs, 1295 participants; low-certainty evidence) [10]	N=131 6.9%/6.1%	N=25 0/0	-
Lamotrigine (LTG)	14 trials (1806 participants) identified. Ataxia 3.34 (99% CI 2.01 to 5.55; 12 trials; 1525 participants; high-certainty evidence); dizziness 2.00 (99% CI 1.52 to 2.64;13 trials; 1768 participants; moderate-certainty evidence); diplopia 3.79 (99% CI 2.15 to 6.68; 3 trials, 944 participants; high-certainty evidence); nausea 1.81 (99% CI 1.22 to 2.68; 12 studies,1486 participants; moderate-certainty evidence) [11]	N=2337 4.2%/0.9% Lower rates of irritability and depressive mood	N=396 3.0%/1.0%	-
Vigabatrine (VGB)	11 trials (756 people) Dizziness/light-headedness (RR 1.74, 95% CI 1.05 to 2.87; 9 studies; low-certainty evidence), fatigue (RR 1.65, 95% CI 1.08 to 2.51; 9 studies; low-certainty evidence), **drowsiness (RR 1.70, 95% CI 1.18 to 2.44; 8 studies)** and **depression (RR 3.28, 95% CI 1.30 to 8.27; 6 studies)** [12]	N=75 10.7%/5.3%	N=30 6.7%/3.3%	-
Lacosamide (LCM)	5 trials (2199 participants) identified Abnormal co-ordination (RR 6.12, 99% CI 1.35 to 27.77), blurred vision (RR 4.65, 99% CI 1.24 to 17.37), diplopia (RR 5.59, 99% CI 2.27 to 13.79), dizziness (RR 2.96, 99% CI 2.09 to 4.20), nausea	N=354 5.1%/3.1%	N=33 9.1%/6.1%	-

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		Adults with epilepsy (80% with DREs)* [2]	Children with epilepsy (80% with DREs)† [3]	
	(RR 2.35, 99% CI 1.37 to 4.02), **somnolence (RR 2.04, 99% CI 1.22 to 3.41)**, vomiting (RR 2.94, 99% CI 1.54 to 5.64) [13]			
Everolimus (EVR)	**-**	-	-	-
Infrequent				
Bromide (Br)	**-**	-	-	-
Felbamate (FLB)	AEs reported by all four trials were headache, dizziness, and nausea [14]	N=184 3.8%/3.3%	N=54 3.7%/1.9%	-
Carbamazepine (CBZ)	-	N=1103 1.8%/0.7% Lower rates of irritability	N=194 4.6%/0.5%	-
Oxcarbazepine (OXC)	4 trials (1593 participants) identified. Ataxia (RR 2.54, 99% CI 0.86 to 7.54; random-effects model; 5 studies; moderate-certainty evidence); and **somnolence (RR 2.03, 99% CI 1.17 to 3.54; random-effects model; 6 studies; low-certainty evidence)** [16]	N=566 2.8%/1.2%	N=166 1.8%/0.6%	
Eslicarbazepine acetate (ESL)	7 trials (2185 participants) identified. Dizziness (RR 2.77, 99% CI 1.85 to 4.15); nausea (RR 2.55, 99% CI 1.39 to 4.67); **somnolence (RR 1.75, 99% CI 1.18 to 2.61);** diplopia (RR 4.07, 99% CI 1.86 to 8.89); and vomiting (RR 2.37, 99% CI 1.19 to 4.74) [17]	-	-	
Phenytoin	-	N=816 2.9%/1.8%	N=109 2.8%/1.8%	
Pregabalin (PGB)	11 trials (3949 participants) identified. Ataxia (RR 3.90, 99% CI 2.05 to 7.42); dizziness (RR 3.15, 99% CI 2.23 to 4.44); fatigue (RR 1.35, 99% CI 0.94 to 1.93;); **somnolence (RR 2.05, 99% CI 1.49 to 2.81)**; and weight gain (RR 4.35, 99% CI 2.34 to 8.11) [18]	N=502 4.4%/2.2%	N=24 8.3%/4.2%	
Gabapentin (GBP)	6 trials identified. Ataxia 2.01 (99% CI 0.98 to 4.11; 3 studies, 787 participants; low-certainty evidence), dizziness 2.43 (99% CI 1.44 to 4.12; 6 studies, 1206 participants; moderate-certainty evidence), fatigue 1.95 (99% CI 0.99 to 3.82; 5 studies, 1161 participants; low-certainty evidence) and **somnolence 1.93 (99% CI 1.22 to 3.06;**	N=606 1.7%/0.8%	N=76 1.3%/1.3%	

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		Adults with epilepsy (80% with DREs)* [2]	Children with epilepsy (80% with DREs)† [3]	
	6 studies, 1206 participants; moderate-certainty evidence) [19]			

Red= significantly associated with increased PBSE rates; green=significantly associated/trend with a decreased PBSE rates
*79.8% (3261/4085) of the study population had seizures that failed to improve with two or more ASMs
†80.4% (741/922) of the study population had seizures that failed to improve with two or more ASMs

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