CNS Drugs

A Practical Guide to the Treatment of Dravet Syndrome with Anti-Seizure Medication

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Supplemental Table S1 Effect of anti-seizure medications (ASMs) used in the treatment of Dravet syndrome on hormonal contraceptives (HCs) and the effect of HCs on ASMs

	Effect of ASM on HC	Effect of HC on ASM
VPA	No clinically relevant effects identified	Possibility of decreased VPA efficacy requiring monitoring when initiating or discontinuing oestrogen-containing contraceptives
CLB	Some HCs are metabolised by CYP3A4, and therefore their effectiveness may be decreased with CLB, which is is a weak CYP3A4 inducer; non-hormonal forms of contraception are recommended	No clinically relevant effects identified
STP	No clinically relevant effects identified	
CBD	No known effects; being evaluated in clinical trial NCT04396730	
FFA	No clinically relevant effects identified	
TPM	Possibility of decreased HC (EE-containing) efficacy at TPM doses of ≥200 mg; non-hormonal forms of contraception are recommended	No clinically relevant effects identified
BR	No clinically relevant effects identified	
LEV	No clinically relevant effects identified	
BRV	No clinically relevant effects identified	
ZNS	No clinically relevant effects identified	
ESM	No clinically relevant effects identified	
PER	Possibility of decreased HC (progestogen-containing) efficacy at PER doses of ≥12 mg/day; non-hormonal forms of contraception are recommended	No clinically relevant effects identified

BR bromide, *BRV* brivaracetam, *CBD* cannabidiol, *CLB* clobazam, *EE* ethinyl estradiol, *ESM* ethosuximide, *LEV* levetiracetam, *PER* perampanel, *STP* stiripentol*, TPM* topiramate*, VPA* valproate, *ZNS* zonisamide

Supplemental Table S2 Practical details of other anti-seizure medications used for the treatment of seizures in patients with Dravet syndrome

	Indication	MOA	Dosage	Safety considerations	ASM drug-drug interactions
LEV	Adjunctive therapy for partial onset seizures with or without secondary generalisation EU: from 1 month of age US: from 4 years of age	Multiple including modulation of synaptic neurotransmitter release via binding to the synaptic vesicle protein SV2A in the brain	Depending on age: Initial: 7–10 mg/kg/day Target: Increase in steps of 7–10 mg/kg/day every 2 weeks Maximum: 30–60 mg/kg/day	Main AEs include: nasopharyngitis, somnolence, headache, fatigue and dizziness. Warning: may cause psychotic symptoms and behavioural abnormalities including irritability and aggressiveness.	None
BRV	Adjunctive therapy for partial onset seizures with or without secondary generalisation EU: from 4 years US: from 16 years	Multiple including binding to the synaptic vesicle protein SV2A in the brain but with greater selectivity and potency than LEV	Initial: 1 mg/kg/day Target: 2 mg/kg/day Maximum: 4 mg/kg/day or 200 mg/day	Main AEs include: dizziness, somnolence, fatigue, nausea, vomiting, constipation, upper respiratory tract infections, cough, influenza, convulsion, vertigo	BRV decreased by 45% with rifampin; BRV decreased by 19%-26% with enzyme-inducing antiseizure medication (e.g., carbamazepine, phenytoin, phenobarbital, primidone) BRV increases phenytoin by 20% and carbamazepine epoxide by 100%
ZNS	Adjunctive therapy for partial onset seizures with or without secondary generalisation EU: from 6 years US: adults	Multiple including blocking sodium channels (changes in T-type Ca2+ currents); binding to the GABA/benzodiazepine receptor ionophore complex (changes in chloride flux)	Initial: 1 mg/kg/day Target: 6–8 mg/kg/day Maximum: 500 mg/day	Main AEs include: somnolence, anorexia, dizziness, headache, nausea, and agitation/irritability. Warning: Serious rashes including cases of Stevens-Johnson syndrome.	The half-life of ZNS is significantly decreased with phenytoin, phenobarbital and carbamazepine, and moderately with VPA ZNS + other carbonic anhydrase inhibitors (e.g TPM) can increase the severity of metabolic

				ZNS is teratogenic in various animals; likely risk to foetus in humans	acidosis and the risk of kidney stones
ESM	Control of absence (petit mal) epilepsy	Suppresses the 3 Hz spike and wave activity associated with absence (petit mal) seizures by lowering thalamic T-Type Ca2+ currents	Initial: 5–10 mg/kg/day Target: 20–40 mg/kg/day Maximum: 1500 mg	Main AEs include: nausea, vomiting, singultus and abdominal pain	ESM may increase phenytoin serum levels VPA may increase ESM levels Carbamazepine increases the plasma clearance of ethosuximide
PER	Adjunctive therapy for partial onset seizures with or without secondary generalisation EU: from 4 years US: from 12 years	Selective, non-competitive antagonist of the AMPA glutamate receptor on post-synaptic neurons	Depending on age: Initial: 1–2 mg/day Target: 4–8 mg/day Maximum: 12 mg/day	Main AEs include: dizziness, somnolence, fatigue, irritability, falls, nausea, weight gain, vertigo, ataxia, headache, vomiting, contusion, abdominal pain, and anxiety Warning: serious psychiatric and behavioural reactions	PER metabolism increased 2-3x (causing lower PER levels) by carbamazepine, oxcarbazepine, and phenytoin

Adapted from the corresponding Summary of Product Characteristics/Prescribing information and Nabbout et al 2021 [102]
AEs adverse events*, BRV* brivaracetam, *ESM* ethosuximide, *EU* European Union, *LEV* levetiracetam, *MOA* mechanism of action, *PER* perampanel, *T-Type Ca2+* threshold calcium currents, *US* United States, *ZNS* zonisamide