Five Considerations when Selecting Adjunctive Treatment for Drug-Resistant Epilepsy

A corrigendum has been published for this infographic, which can be found here.

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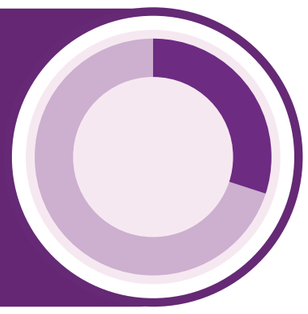
Introduction

DRE is defined as failure of adequate trials of at least two ASMs*[a], used as monotherapy or in combination, to provide sustained seizure freedom[1]

DRE affects approximately **30%** of patients with epilepsy[2]



Pharmacological management of DRE may involve switching medication, or more frequently, the addition of adjunctive medication to a patient's treatment regimen, to try to achieve control of seizures[3]

Adjunctive treatment with additional ASMs requires careful consideration of the potential interactions of the new medication with the existing regimen, as well as suitability of the new medication for the individual patient

Non-pharmacological interventions should also be considered for patients with DRE[3]

Resective surgery eligibility should be considered

Neurostimulation provides an alternative to additional ASMs for adjunctive treatment of DRE

Ketogenic diet has demonstrated effectiveness in children and adolescents with DRE[4]

Key Considerations when Selecting Adjunctive Medications

1. Drug–drug interactions

- **76%** of available ASMs[b] have known interactions with other ASMs
- Dose adjustment of existing or added treatment, and/or monitoring of drug levels, is therefore often required

2. Liver and kidney function

- **75%** of ASMs[c] require dose adjustment, or should be administered with caution in patients with impaired hepatic function
- **70%** of ASMs[d] require dose adjustment, or should be administered with caution in patients with impaired renal function

3. Psychiatric warnings

- All ASMs carry a standard label warning for a class effect of risk of suicidal behaviour and ideation

Psychiatric history may be a relevant consideration when selecting adjunctive anti-seizure treatment

4. Fetal risk

- Birth defects, including neural tube defects, other major malformations, reduced IQ, and neurodevelopmental deficits, have been reported following fetal exposure to valproate[5-8]
- Fetal exposure to topiramate may be associated with increased risk of cleft lip/palate[9]
- Theoretical risk of fetal harm based on teratogenicity data in animals exists for all ASMs, although data on fetal exposure at therapeutic doses in humans are limited for most ASMs

Decisions to add multiple ASMs require careful consideration of risks versus benefits in females of childbearing age

5. Paediatric approval

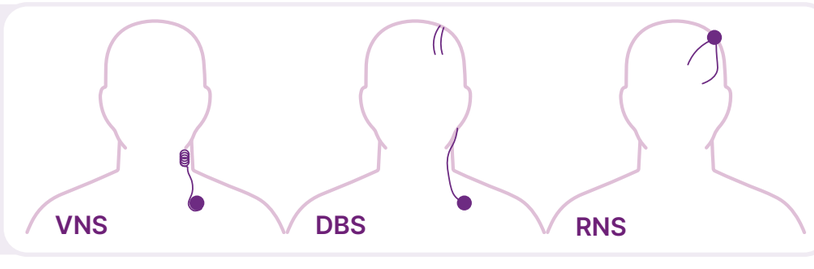
- **68%** of ASMs[b] are approved in patients aged as young as 4 years (and younger for some ASMs)
- VNS implant is the only neurostimulation option approved for paediatric use

Neurostimulation for Adjunctive Treatment of DRE

Adapted from: Shah et al. 2019.[10]

Unlike adjunctive ASMs, the addition of neurostimulation does not carry a risk of drug interactions, and does not require dose adjustment of ASMs to reduce or avoid side effects.

Neurostimulation can be used as adjunctive treatment in patients in whom factors such as impaired liver or kidney function may affect safety/tolerability of pharmacological treatment options



Summary of Key Considerations Relating to Adjunctive Treatment Options for DRE

	DDIs with ASMs	Liver and kidney function		Psychiatric warnings†	Fetal risk	Paediatric approval
		Hepatic adjustment	Renal adjustment			
ASMs*						
Carbamazepine	✓	?	?	♦	✓	✓
Eslicarbazepine acetate	✓	–	✓	♦	✓‡	✓4y
Oxcarbazepine	✓	–	✓	♦	✓	✓2y
Cenobamate	✓	✓	✓	♦	✓‡	–
Lamotrigine	✓	✓	✓	♦	✓‡	✓2y
Phenytoin	✓	✓	?	♦	✓	✓
Primidone	✓	✓	✓	♦	✓	✓
Lacosamide	–	✓	✓	♦	✓‡	✓4y
Zonisamide	✓	✓	✓	♦	✓‡	–
Divalproex sodium	✓	N/A	–	♦	✓	✓10y
Valproic acid	✓	N/A	–	♦	✓	✓10y
Topiramate	✓	?	✓	♦	✓	✓2y
Tiagabine	✓	✓	–	♦	✓‡	✓12y
Vigabatrin	✓	?	✓	♦	✓‡	✓10y
Felbamate	✓	N/A	✓	♦	✓‡	✓2y
Perampanel	✓	✓	✓	♦	✓‡	✓12y
Levetiracetam	–	–	✓	♦	✓‡	✓4y
Brivaracetam	✓	✓	–	♦	✓‡	✓1m
Fenfluramine	✓	✓	✓	♦	✓‡	✓2y
Gabapentin	–	–	✓	♦	✓‡	✓3y
Pregabalin	–	–	✓	♦	✓‡	✓4y
Clorazepate	?	?	?	♦	✓	✓9y
Clobazam	?	✓	–	♦	✓‡	✓2y
Diazepam	✓	?	?	♦	✓	✓6m
Cannabidiol	✓	✓	–	♦	✓‡	✓2y
Neurostimulation Devices (implantable)						
VNS	–	–	–	◇	?#	✓4y
RNS	–	–	–	◇	?#	–
DBS	–	–	–	♦	?#	–

Key

✓	Indicates that potential for DDIs, recommendations to consider dose adjustment according to hepatic/renal function, fetal risk warnings, or paediatric approval, are stated on product label
–	Indicates that product label states absence of DDIs, no requirement for hepatic/renal adjustment, or that approval is for patients aged ≥18 years (lack of paediatric approval)
?	Indicates that product label does not specify whether DDIs, hepatic/renal function, or fetal risk warnings, are relevant considerations for that product when used for epilepsy indications
N/A	Indicates consideration is not applicable (for products that are contraindicated in patients with hepatic dysfunction)
*	ASMs approved in the USA for indications including epilepsy, seizure types including focal-onset (partial) and generalised seizures, or seizures associated with Lennox–Gastaut syndrome or Dravet syndrome
†	All ASMs carry a standard warning for risk of suicidal behaviour and ideation
‡	Risk of fetal harm based on animal teratogenicity data
#	Safety and effectiveness have not been established in pregnant women
xy/m	Approved in paediatric patients aged >x years/months, where minimum age is stated on product label
◇	A lack of presence of psychiatric warnings are stated on the product label
♦	Presence of psychiatric warnings are stated on the product label

Abbreviations

ASM: anti-seizure medication; **DBS**: deep brain stimulation; **DDI**: drug–drug interaction; **DRE**: drug-resistant epilepsy; **N/A:** not applicable; **RNS**: responsive neurostimulation; **VNS**: vagal nerve stimulation.

[a]Appropriately chosen medications, used as directed at an efficacious dosage and tolerated

[b]n=25 FDA-approved ASMs (listed in Table) indicated for the treatment of epilepsy, seizure types including focal-onset (partial) and generalised seizures, or seizures associated with Lennox–Gastaut syndrome or Dravet syndrome

[c]n=20; excludes ASMs that are contraindicated in patients with hepatic dysfunction and those for which data on pharmacokinetics in patients with hepatic impairment are not available

[d]n=23; excludes ASMs for which data on pharmacokinetics in patients with renal impairment are not available

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