Update to SIGN Guideline SIGN 159: Epilepsies in Children and Young People - Section 5: Pharmacological Therapies consultation

COMMENTS RECEIVED FROM EXTERNAL REFEREES AND OTHERS

All reviewers submitted declarations of interests which were viewed prior to the addressing of comments.

Invited reviewers			**Type of response and declared interests**
ES	Elma Stephen	Consultant Paediatric Neurologist, NHS Grampian	*Individual response.* Personal financial interests Consultancy fees paid to self by Nutricia in June 2025 for organising and speaking at Nutricia- sponsored symposium on complex epilepsies.
SP	Sasha Peacock	Epilepsy Nurse Specialist, NHS Tayside	*Individual response.* Nothing declared.
Open consultation			**Type of response and declared interests**
DS	Domenico Serino	Consultant Paediatric Neurologist, Royal Aberdeen Childrens Hospital, NHS Grampian	*Individual response.* Nothing declared.
SB		Simona Balestrini, Consultant in Adult and Child Neurology, UCLH/Meyer Children's Hospital (Florence, Italy) commenting on behalf of Epilepsy Society	*Individual response.* Personal financial interests Advisory board, Biocodex – topic specific. Travel support, JazzPharma – non-topic specific.
YE		Catherine Hodder, Head of Voice, Policy and Influencing commenting on behalf of Young Epilepsy	*Group response*. Nature and purpose of your group or organisation Charity supporting children and young people with epilepsy in the UK.

			How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/status/productivity? Draft recommendations in this SIGN guideline will improve clarity for children and young people with epilepsy in Scotland. Updated recommendations may affect the information Young Epilepsy provides on its website.

General/Additional comments:				
Section	*Reviewer*	*Comment*	*Development group response*	*Editorial response*
	ES	Very useful reference - this update is timely!	Thank you	✔
	SB	This draft provides a comprehensive and well-structured overview of antiseizure medication (ASM) use in paediatric epilepsy, incorporating regulatory safety measures (MHRA), NICE-aligned recommendations, and syndrome-specific guidance. The emphasis on shared decision-making and young people's perspectives is commendable and aligns with modern standards of patient-centred care. However, several areas would benefit from recalibration in light of recent high-quality evidence. In particular: • Valproate – male fertility and reproductive risk framing • Levetiracetam – comparative effectiveness and evidentiary strength • Dravet syndrome –relative positioning of fenfluramine and cannabidiol These issues do not undermine the overall structure of the guideline but warrant refinement to ensure that recommendations reflect the strongest available comparative data and avoid perpetuating legacy prescribing patterns unsupported by robust evidence.	Thank you. Specific comments are addressed in the sections below.	✔ ✔
Section 5.1: Antiseizure medications				
	DS	I agree with the guideline content.	Thank you	✔

	ES	Under Information point, include 'Formulation'. 'With children, concordance to ASMs can be a significant problem and it is important. Recognise this to overcome potential barriers'- this does not read well- do you mean adherence? Concordance means 'agreement/ consistency between things. 'All children with complex epilepsies should be managed in, or with advice from, a tertiary epilepsy clinic.' have you provided guidance on what would fall under 'complex epilepsies' - may need to consider re-phrasing as this is not the same as a medically refractory epilepsy.	Added Agree. While in this situation concordance refers to agreement between clinician and patient, in paediatrics adherence is more commonly used and appropriate as parents are expected to adhere to advice on medication for their child. Amended to adherence. We have added the following sentence to the definitions in section 1.2.2: Complex epilepsies are defined as epileptic encephalopathies, structural abnormalities or where there is an additional neurological comorbidity or neurodevelopmental disorder, and require advice from a tertiary epilepsy clinic or specialist input (see SPEN Pathway 3).	✔ ✔ ✔
	SP	Nothing to add really - very well explained. As a service, we do ensure we cover possible side effects and how long to expect these to last once commencing treatment. We also check-in with families a few weeks after starting to see how they are doing.	Thank you	✔
5.1.1	SB	The draft appropriately reflects current MHRA precautionary measures regarding valproate use in individuals under 55 years of age and in those of childbearing potential. However, the discussion of male reproductive risk appears to rely on earlier assumptions derived primarily from animal studies and limited observational data. A large retrospective cohort study published in 2025 (Mbizvo et al., Nature Communications) examined over 91,000 valproate-exposed men using international real-world healthcare data with propensity score matching and	While we agree we need to align with MHRA advice and we signpost to their website for the most current advice. We do state in 5.1.1 that it is a precaution for men to use contraception We have added the following sentence:	✔ ✔

		survival analysis. This study found no significant association between valproate exposure and male infertility, testicular hypofunction, testicular atrophy, or abnormal semen parameters. While regulatory precautions remain in force, the guideline should distinguish between regulatory risk-minimisation policies, and current empirical evidence regarding male infertility outcomes. Failure to incorporate this distinction risks overstating the strength of evidence for male infertility and may contribute to therapeutic hesitancy disproportionate to documented risk. I would recommend to include a statement acknowledging that recent large-scale human data do not support a measurable increase in male infertility, and to clarify that existing MHRA restrictions are precautionary and relate to broader reproductive risk considerations rather than established infertility outcomes. I would also explicitly state that valproate remains an important option in children not at risk of pregnancy (e.g., boys and prepubertal girls), provided regulatory safeguards are met.	This risk was raised following evidence from animal studies but has not been replicated in large-scale human studies. We have added the following sentences: Valproate remains a clinically effective option for treating children with epilepsies. It is important to have full discussion and consideration of safeguards with parents or young people before use.	✔
5.1.1	YE	We welcome the emphasis on discussing available treatment options with the child and their family, taking into consideration potential side effects. It is important that young people understand their options and know what to do if they have any concerns regarding side effects. The section on valproate should include signposting to the following guidance. These documents include further information on age-specific prescribing and the definition of who can be considered a second specialist:	We have added the following sentence Further advice on prescribing valproate to patients under the age of 18 is available from the Royal College of Paediatrics and Child Health, and the British Paediatric Neurology Association https://bpna.org.uk/.	✔

		'Update for Valproate Prescribing in Paediatric Neurology' (BPNA, OPEN UK and RCPCH) [https://www.rcpch.ac.uk/sites/default/files/2024-02/1._bpeg_open_uk_rcpch_documenton_prescribing_valproate_020124_final_1.pdf] 'Prescribing valproate to female patients under 18 years of age' (BPNA & RCPCH) [https://www.rcpch.ac.uk/sites/default/files/2024-02/2._february2024_prescribing_valproate_to_female_patients_under_18_years_of_age.pdf]		
Section 5.2: Focal epilepsy				
	DS	I agree with the guideline content.	Thank you	✔
5.2.1 **5.2.2**	ES	Section 5.2.1 - has evidence for Brivaracetam use been reviewed and can it been included in the recommendations for monotherapy? This may be more commonly prescribed than Lacosamide and Zonisamide. Section 5.2.2 - typo in last recommendation- should be '.....third line adjunctive therapies if second-line therapies are considered unsuccessful.....'.	NICE did not find evidence for the use of brivaracetam as first line therapy. Rationale from NICE for 2nd line adjunctive: From the evidence, it was difficult to determine the most effective add-on treatment for people with focal epilepsy that has failed to respond to monotherapy. The evidence showed that a number of antiseizure medications are effective compared with placebo for more than 50% reduction in seizure frequency rate: brivaracetam, carbamazepine, eslicarbazepine acetate, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate and zonisamide. Typo amended, thank you.	✔ ✔
	SB	The draft aligns with NICE in presenting levetiracetam as a first-line option across several epilepsy syndromes. However, emerging and established high-quality evidence challenges this	Our recommendation gives levetiracetam as a first-line option, but we have also included carbamazepine as it is better tolerated in children than adults. We have also included a caution around mood with levetiracetam use.	✔

		positioning, particularly in initial monotherapy settings. Key considerations include: - SANAD II (focal epilepsy): Levetiracetam was neither clinically nor cost-effective compared with lamotrigine and zonisamide. - SANAD II (generalised/unclassified epilepsy): Levetiracetam did not meet non-inferiority criteria versus valproate for 12-month remission. We have conducted a recent meta-analysis of 25 RCTs (n = 4,070), currently under review in Neurology, demonstrating benefit versus placebo as adjunctive therapy, but no advantage over active comparators and potential inferiority in certain epilepsy subgroups and when restricted to low risk-of-bias trials. Only a minority of LEV trials were at low risk of bias. I suggest rebalancing language to clarify that levetiracetam demonstrates efficacy versus placebo but has not consistently outperformed established ASMs in comparative trials. I think important to reference SANAD II explicitly in focal and generalised epilepsy sections, and strengthen warnings regarding behavioural adverse effects in paediatric populations. I would avoid positioning LEV as a default first-line agent based solely on tolerability or ease of use.		
	SP	Explained well. Perhaps we will see Cenobamate added in as an option now for focal epilepsy? Not a first line but as an adjunctive?	We cannot include this at the moment as it is not licensed yet.	✔
	YE	The recommendations, language and presentation are appropriate.	Thank you	✔
Section 5.3: Generalised epilepsy				

	DS	I agree with the guideline content.	Thank you	✔
	ES	Agree.	Thank you	✔
	SP	Again well explained but for absence seizures, recommendation of using SV as first line treatment now goes against updated MHRA guidance.	We have recommended ethosuximide as 1st line treatment. Sodium valproate remains clinically effective. We have included a good practice point signposting to the MHRA guidance for SV.	✔
	YE	The recommendations, language and presentation are appropriate.	Thank you	✔
Section 5.4: Lennox-Gastaut Syndrome				
	DS	I agree with the guideline content.	Thank you	✔
	ES	Section 5.4 Agree - suggest re-arrange paragraph re cannabidiol discussion to be paragraph 3 (rather than paragraph 7) followed by NICE recommendation on Fenfluramine as it flows better and logically for the reader.	We prefer to keep the advice from NICE together as it shows what they recommend 1st, 2nd and 3rd line. The following paragraphs are structured to show benefits, harms and cost effectiveness.	✔
	SP	Well explained, nothing to add.	Thank you	✔
	YE	The recommendations, language and presentation are appropriate.	Thank you	✔
Section 5.5: Infantile Spasms/West Syndrome				
	DS	I would highlight that applying the ICISS protocol is no longer recommended.	Rec amended to say mono or combined therapy can be considered. Hormonal treatment (adrenocorticotropic hormone, tetracosactide or prednisolone) **with or without** vigabatrin could be considered as the first-line treatment for IESS.	✔
	ES	Section 5.5- suggest using ILAE terminology and replacing title Infantile spasms/ West syndrome with 'Infantile Epileptic Spasms Syndrome'.	Agree, change.	✔

		In recommendations, I think you should say 'hormonal treatment, vigabatrin or combined hormonal treatment and vigabatrin should be considered as first line for epileptic spasms. in practice, a large number of centres use the ICISS protocol which is combined therapy with both steroid s and Vigabatrin.	Either option is viable so we have amended the recommendation to be open to preference: Hormonal treatment (adrenocorticotropic hormone, tetracosactide or prednisolone) **with or without** vigabatrin could be considered as the first-line treatment for IESS.	✔
	SP	Well explained - we generally trial steroid treatment first as well as nitrazepam over Vigabatrin due to potential side visual problems.	We have worded the recommendation so that therapies can be tailored to the individual patient.	✔
	YE	The recommendations, language and presentation are appropriate.	Thank you	✔
Section 5.6: Tuberous Sclerosis				
	DS	I agree with the guideline content.	Thank you	✔
	ES	Agree, is it worth considering recommendations on when everolinus should be withdrawn?	This is an individualised, patient-specific decision.	✔
	SP	Currently one patient on Everolimus so not much experience or comment to make.	Thank you	✔
	YE	The recommendations, language and presentation are appropriate.	Thank you	✔
Section 5.7: Dravet Syndrome				
	DS	I agree with the guideline content.	Thank you	✔
	ES	Dravet syndrome international consensus guidelines and expert groups now recommend Fenfluramine in preference to Cannabidiol- this does not seem to come out well in the recommendations.	There is not extensive evidence for therapies. The number of children in Scotland with DS is low. They are managed in specialist centres. We prefer to leave the recommendations with a wide choice of options so that the clinicians	✔

			involved can apply their expertise and provide individualised care.	
	SB	The draft lists appropriate treatment options for Dravet syndrome (DS), but I believe the contraindication of sodium channel–blocking ASMs is not emphasised with sufficient strength. An International expert consensus (https://pubmed.ncbi.nlm.nih.gov/35490361/) clearly states that carbamazepine, oxcarbazepine, and lamotrigine are generally contraindicated for chronic maintenance therapy in DS, as they may exacerbate seizures and worsen developmental outcomes. Additionally: valproate remains first-line, clobazam is typically second-line, stiripentol and fenfluramine are recommended early in sequencing. Cannabidiol is generally positioned after these options. Chronic phenytoin is discouraged, though IV phenytoin remains acceptable for status epilepticus. The draft appropriately includes fenfluramine but may understate the strength of its evidence base relative to other adjunctive therapies. Three phase 3 RCTs demonstrate 34–72% placebo-adjusted reduction in monthly convulsive seizure frequency, 41–73% ≥50% responder rates, durable long-term benefit in extension studies. No observed valvular heart disease under mandated monitoring protocols. A network meta-analysis (https://pubmed.ncbi.nlm.nih.gov/38427284/) suggested greater convulsive seizure reduction with fenfluramine and stiripentol compared with cannabidiol. I suggest considering elevation of fenfluramine to early second-line positioning in DS, noting also evidence of improvements in executive function and quality-of-life domains, but maintain clear echocardiographic monitoring guidance and clarify dose adjustments when combined with stiripentol.	There is not extensive evidence for therapies. The number of children in Scotland with DS is low. They are managed in specialist centres. We prefer to leave the recommendations with a wide choice of options so that the clinicians involved can apply their expertise and provide individualised care.	✔

		Cannabidiol is supported by high-quality RCTs and long-term extension data, but its relative efficacy appears modest compared with fenfluramine and stiripentol in indirect comparisons. Also important to emphasise CYP2C19 interaction with clobazam, highlight transaminase elevation risk with concomitant valproate, encourage proactive dose adjustment of clobazam if sedation emerges.		
	SP	Well explained, no comments to add.	Thank you	✔
	YE	The language in this section and recommendation should make clear that clobazam and stiripentol are recommended as a 'triple therapy' with sodium valproate. The recommendation related to fenfluramine states that it could be considered as an adjunctive therapy 'in conjunction with clobazam'. This is the case for cannabidiol, but not for fenfluramine.	We have amended the recommendation to: Stiripentol and clobazam could be considered as an adjunctive therapy with sodium valproate for children (3 years and older) with Dravet syndrome whose seizures are poorly controlled with sodium valproate alone.	✔