



UNIVERSIDADE FEDERAL DE SANTA CATARINA
CENTRO DE CIÊNCIA, TECNOLOGIAS E SAÚDE
DEPARTAMENTO DE CIÊNCIAS MÉDICAS
CURSO DE MEDICINA

João Cândido Spezia de Souza
Marina Ilha Zimmermann

**Estimulação do nervo vago em pacientes pediátricos com a síndrome de
Lennox-Gastaut: uma revisão sistemática**

Araranguá
2026

João Cândido Spezia de Souza
Marina Ilha Zimmermann

**Estimulação do nervo vago em pacientes pediátricos com a síndrome de
Lennox-Gastaut: uma revisão sistemática**

Trabalho de Conclusão do Curso de Graduação em
Medicina do Centro de Ciências, Tecnologias e
Saúde da Universidade Federal de Santa Catarina
como requisito para a obtenção do título de
Bacharel em Medicina.

Orientadora: Profa. Dra. Ana Carolina L. Cancelier
Co-orientadora: Profa. Dra. Maruí W. Corseuil
Giehl

Araranguá
2026

Zimmermann, Marina Ilha

Estimulação do nervo vago em pacientes pediátricos com a síndrome de Lennox-Gastaut : Uma revisão sistemática / Marina Ilha Zimmermann, João Cândido Spezia de Souza ; orientadora, Ana Carolina Lobor Cancelier, coorientador, Maruí W. Corseuil Giehl, 2026.

102 p.

Trabalho de Conclusão de Curso (graduação) - Universidade Federal de Santa Catarina, Campus Araranguá, Graduação em Medicina, Araranguá, 2026.

Inclui referências.

1. Medicina. 2. Síndrome de Lennox-Gastaut. 3. Estimulação do Nervo Vago. 4. Pediatria . 5. Epilepsia refratária. I. Souza , João Cândido Spezia de. II. Cancelier, Ana Carolina Lobor . III. Giehl, Maruí W. Corseuil . IV. Universidade Federal de Santa Catarina. Graduação em Medicina. V. Título.

João Cândido Spezia de Souza e Marina Ilha Zimmermann

**Estimulação do nervo vago em pacientes pediátricos com a síndrome de
Lennox-Gastaut: uma revisão sistemática**

Este Trabalho de Conclusão de Curso foi julgado adequado para obtenção do título de
“Bacharel em Medicina” e aprovado em sua forma final pelo Curso de Graduação em
Medicina do Centro de Ciências, Tecnologias e Saúde da Universidade Federal de Santa
Catarina

Araranguá, 15 de junho de 2026.



Coordenação do Curso
Profa. Tamiris Dal Bó Martinello

Banca examinadora



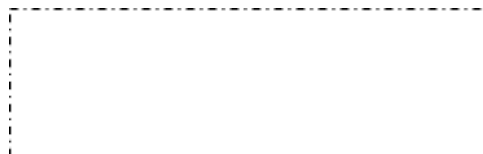
Profª Dra. Ana Carolina Lobor Cancelier
Orientadora



Victor Seabra Lima Prado Costa

Avaliador

Instituição USP



Profª. Dra. Camila Bellettini Hirsch

Avaliador

Instituição UFSC

Araranguá, 2026.

Dedicamos este trabalho a quem nos guiou e acolheu até aqui:
aos ainda presentes, aos não mais.

AGRADECIMENTOS

Somos extremamente gratos aos nossos professores, em especial aos que nos guiaram neste projeto com afinco e dedicação - Prof^a Dra. Ana Carolina Lobor Cancelier como orientadora e Prof^a. Dra. Maruí W. Corseuil Giehl como coorientadora, bem como a banca examinadora Victor Seabra Lima Prado Costa, Prof^a. Dra. Camila Bellettini Hirsch e Prof^a Bianca Kelem Mazetto.

Agradecemos àqueles que nos trouxeram ao mundo e nos guiam na busca por nos tornarmos médicos éticos e humanos — uma extensão do que aprendemos em casa: Lisiane, João, Fatima e Kleber.

Nossa gratidão se estende a quem esteve presente por escolha, nos melhores e piores dias dessa jornada: nossos cônjuges, Emanuelle e Diego.

Aos familiares, em especial Marina, Liliane e Cleonice por fazerem parte da nossa formação em diversos aspectos.

Aos amigos que se tornaram casa, família e acolhimento no processo de quem se despediu do seu ninho: Natan, Darlos, Luis, Anderson, Wilson, Vitória, Thainá, Jordan, Marcos, Beatriz, Yasmin, Ana, Marina, Laís, Elias, Karen, Scheila, Guilherme, Felipe, Luiz e Vinícius.

Por fim, agradecemos aos ausentes que, mesmo de longe, vibram por nossas vitórias e nutrem nossa alma na esperança de que nos cruzemos, algum dia, para além desta vida: Catarina, Izabel, Alcides, Cyrce e Beatriz.

“Eu fico com a pureza da resposta das crianças.

É a vida, é bonita e é bonita.”

— Gonzaguinha (1982)

RESUMO

Esta pesquisa avalia a efetividade e a segurança da Estimulação do Nervo Vago (ENV) no tratamento da Síndrome de Lennox-Gastaut (SLG) farmacorresistente em pacientes pediátricos. O estudo utiliza como método uma revisão sistemática da literatura, fundamentada em estudos observacionais e análise de séries de casos, seguida de aplicação do instrumento ROBINS-I para a avaliação do risco de viés. Os resultados demonstram que, na amostra total combinada de 456 pacientes provenientes dos estudos incluídos, 374 apresentaram redução superior a 50% na frequência das crises epiléticas após a ENV, além do registro de casos de remissão completa. A análise evidencia que a intervenção demonstra maior efetividade em crises do tipo atônicas (*drop attacks*), seguidas pelas crises tônicas e de ausência. No âmbito dos desfechos secundários, a pesquisa aponta melhorias qualitativas significativas no estado de alerta, na atenção e na qualidade do sono dos pacientes. É válido ressaltar que, embora a intervenção seja segura, os estudos apresentam elevado risco de viés no domínio de mensuração de desfechos, principalmente pela inviabilidade do cegamento em procedimentos cirúrgicos e pela subjetividade dos relatos dos cuidadores. Observa-se que a heterogeneidade das respostas clínicas decorre da assimetria nos parâmetros de estimulação e das variações nos quadros clínicos iniciais. Conclui-se que a ENV apresenta resultados que sugerem potencial utilidade no manejo da SLG. Embora o cenário ideal demande ensaios clínicos randomizados com amostras representativas e exclusivas para a síndrome e protocolos padronizados de estimulação, entende-se que existe uma limitação metodológica tratando-se de uma síndrome rara. Portanto, evidencia-se a importância desta revisão sistemática a fim de estimular decisões clínicas individualizadas e assertivas no manejo destes pacientes.

Palavras-chave: Pediatria; Epilepsia; Síndromes epiléticas; Síndrome de Lennox-Gastaut; Neuromodulação; Estimulação do nervo vago.

ABSTRACT

This study evaluates the effectiveness and safety of Vagus Nerve Stimulation (VNS) in the treatment of drug-resistant Lennox-Gastaut Syndrome (LGS) in pediatric patients. The method employed is a systematic literature review based on observational studies and case series analysis, followed by the application of the ROBINS-I tool to assess the risk of bias. The results demonstrate that, within the combined total sample of 456 patients from the included studies, 374 showed a reduction of over 50% in epileptic seizure frequency following VNS, alongside reported cases of complete remission. The analysis highlights that the intervention shows greater effectiveness in atonic seizures (drop attacks), followed by tonic and absence seizures. Regarding secondary outcomes, the research points to significant qualitative improvements in the patients' alertness, attention, and sleep quality. It is worth noting that, although the intervention is safe, the studies present a high risk of bias in the outcome measurement domain, mainly due to the infeasibility of blinding in surgical procedures and the subjectivity of caregiver reports. It is observed that the heterogeneity of clinical responses stems from asymmetry in stimulation parameters and variations in initial clinical presentations. In conclusion, VNS yields results that suggest potential utility in the management of LGS. While the ideal scenario would require randomized clinical trials with representative and exclusive samples for the syndrome, as well as standardized stimulation protocols, it is understood that methodological limitations exist when dealing with a rare syndrome. Therefore, the importance of this systematic review is highlighted in order to encourage individualized and assertive clinical decisions in the management of these patients.

Keywords: Pediatrics; Epilepsy; Epileptic syndromes; Lennox-Gastaut Syndrome; Neuromodulation; Vagus nerve stimulation.

LISTA DE FIGURAS

Figura 1 - Fluxograma PRISMA	19
Figura 2 - Risco de viés	23

LISTA DE TABELAS

Tabela 1 - Dados gerais dos artigos selecionados	20
Tabela 2 - Resultados relativos ao número de crises de todas as modalidades após a ENV.....	25

LISTA DE ABREVIATURAS E SIGLAS

AAN	American Academy of Neurology
DA	Drop attack
ECR	Ensaio Clínico Randomizado
EEG	Eletroencefalograma
ENV	Estimulação do Nervo Vago
HM	Honeymoon
Hz	Hertz
ILAE	Liga Internacional Contra a Epilepsia
JCSS	João Cândido Spezia de Souza
mA	Mili Ampère
MeSH	Medical Subject Headings
MIZ	Marina Ilha Zimmermann
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PROSPERO	International Prospective Register Of Systematic Reviews
ROBINS I	Risk of Bias In Non-Randomized Studies Of Interventions
SLG	Síndrome de Lennox Gastaut

SUMÁRIO

1	INTRODUÇÃO.....	16
2	METODOLOGIA.....	18
2.1	CRITÉRIOS DE ELEGIBILIDADE.....	18
2.2	ESTRATÉGIA DE BUSCA.....	18
2.3	SELEÇÃO, EXTRAÇÃO, SÍNTESE E ANÁLISE DE DADOS.....	18
2.4	AVALIAÇÃO DO RISCO DE VIÉS.....	19
3	RESULTADOS.....	20
3.1	SELEÇÃO DOS ESTUDOS.....	20
3.2	CARACTERÍSTICAS DOS ESTUDOS.....	21
3.3	AVALIAÇÃO DO RISCO DE VIÉS DOS ESTUDOS.....	24
3.4	DESFECHOS PRIMÁRIOS.....	26
3.4.1	VARIAÇÃO DO NÚMERO DE CRISES APÓS A ENV.....	26
3.4.1.1	<i>VISÃO GERAL DA AMOSTRA E CATEGORIZAÇÃO DA RESPOSTA.....</i>	<i>26</i>
3.4.1.2	<i>RESULTADOS A CURTO PRAZO (1 A 6 MESES PÓS ENV).....</i>	<i>29</i>
3.4.1.3	<i>RESULTADOS A MÉDIO PRAZO (9 A 12 MESES PÓS-ENV).....</i>	<i>31</i>
3.4.1.4	<i>RESULTADOS A LONGO PRAZO (>12 A ≥24 MESES PÓS-ENV).....</i>	<i>31</i>
3.4.1.5	<i>DESFECHOS VARIÁVEIS E ACHADOS INDEPENDENTES.....</i>	<i>32</i>
3.4.2	RESPOSTA POR TIPO E QUALIDADE DAS CRISES.....	33
3.4.2.1	<i>CRISES ATÔNICAS E DE QUEDA (DROP ATTACKS - DA).....</i>	<i>33</i>
3.4.2.2	<i>CRISES TÔNICO E TÔNICO-CLÔNICAS GENERALIZADAS.....</i>	<i>34</i>
3.4.2.3	<i>CRISES DE AUSÊNCIA E MIOCLÔNICAS.....</i>	<i>34</i>
3.4.2.4	<i>OUTROS SUBTIPOS E ASPECTOS QUALITATIVOS DAS CRISES.....</i>	<i>35</i>
3.5	DESFECHOS SECUNDÁRIOS.....	35
3.5.1	ESTADO DE ALERTA, ATENÇÃO E SONO.....	36
3.5.2	COMUNICAÇÃO, COMPORTAMENTO E DESEMPENHO ESCOLAR.....	36
3.5.3	PARÂMETROS CLÍNICOS E TERAPÊUTICOS ADICIONAIS.....	37
3.6	EFEITOS ADVERSOS.....	37
3.6.1.	ALTERAÇÕES DE VOZ E SINTOMAS RESPIRATÓRIOS.....	37

3.6.2	COMPLICAÇÕES NO SÍTIO CIRÚRGICO E INFECÇÕES.....	38
3.6.3	DISFAGIA, SIALORREIA E OUTROS EVENTOS SISTÊMICOS.....	38
3.6.4.	ÓBITOS REGISTRADOS.....	39
4	DISCUSSÃO.....	40
4.1	QUANTO À EFETIVIDADE: UMA AVALIAÇÃO DE NÚMERO E QUALIDADE DAS CRISES.....	40
4.2	QUANTO AOS DESFECHOS SECUNDÁRIOS.....	42
4.3	QUANTO AOS EFEITOS ADVERSOS DA ESTIMULAÇÃO DO NERVO VAGO	42
4.4	LIMITAÇÕES E EXPECTATIVAS.....	43
5	CONCLUSÃO.....	46
	REFERÊNCIAS.....	47

1 INTRODUÇÃO

As epilepsias da infância constituem uma das condições neurológicas crônicas mais comuns nessa fase da vida e, em muitos casos, apresentam curso relativamente favorável. Entretanto, a síndrome de Lennox Gastaut (SLG) contrapõe-se a esse padrão, por se tratar de uma encefalopatia epiléptica grave com impacto importante no desenvolvimento da criança (1).

A síndrome de Lennox Gastaut é uma patologia da faixa etária pediátrica caracterizada por múltiplas crises convulsivas, frequentemente resistentes ao tratamento medicamentoso, com padrões específicos no eletroencefalograma (EEG), como complexos de ondas lentas e pontiagudas ou atividade paroxística generalizada rápida associada ainda com deficiência intelectual (2).

A prevalência da encefalopatia de Lennox-Gastaut é estimada em 1 a 2% de todos os pacientes com epilepsias (2). Sua etiologia é heterogênea, podendo envolver causas de origem genética, estrutural ou metabólica, responsáveis por cerca de 65 a 75% dos casos, nos demais, a causa permanece desconhecida (2).

Embora o início dos sintomas ocorra predominantemente na infância, a SLG apresenta repercussões ao longo da vida, uma vez que as crises tendem a persistir de forma refratária e podem se associar a sequelas cognitivas, como deficiência intelectual e funcional, além de problemas comportamentais (3). Estudo de coorte retrospectiva que acompanhou 38 adultos com SLG diagnosticada na infância apontou que todos os pacientes tiveram três ou mais tipos de crises epiléticas ao longo da história clínica, dentre elas: ausências atípicas, crises tônicas, crises tônico-clônicas generalizadas, crises focais e mioclônicas, todas resistentes a medicamentos (3).

Diante da refratariedade de tratamento com fármacos, a literatura descreve diferentes alternativas terapêuticas não farmacológicas para o controle da SLG (4,5,6,7,8,9,10). As principais intervenções incluem a calosotomia, a estimulação do nervo vago (ENV) e a dieta cetogênica. A secção do corpo caloso tem demonstrado maior efetividade do que a dieta cetogênica na redução da frequência de convulsões em pacientes com LGS (11). No entanto, trata-se de um processo cirúrgico frequentemente associado a efeitos adversos, sobretudo no período pós-operatório imediato (11,12). Em contrapartida, a ENV tem sido relacionada a melhora no estado de alerta, da qualidade de vida, além de apresentar um perfil de segurança

predominantemente favorável, com menor ocorrência de complicações graves quando comparada à calosotomia (11,13,14).

A ENV consiste no implante cirúrgico de um dispositivo que promove a estimulação elétrica intermitente do nervo vago, com o objetivo de modular a atividade neuronal e, conseqüentemente, reduzir a frequência, a intensidade e a gravidade das crises epiléticas (15,16). O dispositivo, implantado geralmente na região torácica, é conectado ao nervo vago na região cervical e funciona emitindo pulsos elétricos em intervalos regulares, contribuindo para o controle das descargas elétricas anormais no cérebro (15,17,18). Estudos recentes têm demonstrado que a ENV parece ser eficaz em pacientes com SLG, com taxas de resposta definidas como redução igual ou superior a 50% na frequência das crises, variando entre 54% e 66,7% em diferentes análises (16,19).

Apesar do uso crescente da ENV, ainda há lacunas quanto a magnitude de seu benefício especificamente em pacientes pediátricos com SLG. Nesse contexto, esta revisão sistemática teve como objetivo avaliar a efetividade da ENV na redução das crises epiléticas em pacientes com SLG, considerando a frequência, o tipo de crise e a evolução dos sintomas pós intervenção. Adicionalmente, buscou-se analisar a ocorrência de efeitos adversos e a tolerabilidade da ENV em crianças e adolescentes com SLG.

2 METODOLOGIA

Esta revisão sistemática de literatura foi desenvolvida conforme as recomendações do Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (20) e registrada na base de dados de revisões sistemáticas PROSPERO (CRD420251151322).

2.1 CRITÉRIOS DE ELEGIBILIDADE

Embora os Ensaios Clínicos Randomizados (ECRs) fossem elegíveis, nenhum estudo com esse delineamento atendeu aos critérios estabelecidos, assim, coortes em séries de casos, realizados em crianças com mais de um mês, mas menores de 18 anos diagnosticadas com SLG e que realizaram ENV foram inclusos. Os estudos deveriam apresentar dados sobre as crises epiléticas e ocorrência de eventos adversos. Foram excluídos estudos duplicados, publicações cujo foco principal fossem outras síndromes epiléticas, revisões narrativas, editoriais, estudos experimentais em modelos animais, bem como publicações sem acesso ao texto completo.

2.2 ESTRATÉGIA DE BUSCA

Foram utilizadas as seguintes bases de dados: MEDLINE (via Pubmed), Embase, Cochrane Library e Web of Science sem restrição de idiomas e de tempo por tratar-se de uma temática com bibliografia escassa.

Para a pesquisa documental, os descritores selecionados se basearam no Medical Subject Headings (MeSH). A chave de busca foi adaptada para as devidas especificidades de cada base de dados. As palavras-chave utilizadas no MEDLINE são as seguintes: (Child OR children OR pediatric OR infant OR childhood) AND (Gastaut OR LGS) AND vagus.

2.3 SELEÇÃO, EXTRAÇÃO, SÍNTESE E ANÁLISE DE DADOS

Aplicando a metodologia PRISMA (20), por meio da estratégia PICOS, definiram-se os seguintes parâmetros: população composta por crianças de 1 mês a

18 anos com diagnóstico confirmado de Síndrome de Lennox-Gastaut (SLG), conforme os critérios da Liga Internacional Contra a Epilepsia (ILAE), caracterizados por crises múltiplas, eletroencefalograma (EEG) com padrão de ponta-onda lenta e comprometimento cognitivo; intervenção baseada na estimulação do nervo vago; comparação com tratamento farmacológico, dieta cetogênica e abordagens cirúrgicas distintas da estimulação do nervo vago (ENV); desfechos relacionados à resposta clínica, redução da frequência de crises e diminuição da taxa de efeitos colaterais; e, por fim, inclusão de estudos com delineamento do tipo ensaios clínicos randomizados (ECRs), coortes prospectivas e séries de casos.

A seleção de artigos foi feita usando a estratégia acima descrita e a extração de dados foi conduzida de forma independente pelos dois autores (JCSS e MIZ). Divergências ocasionais foram resolvidas através de consenso entre pares e orientadoras. O software Zotero foi utilizado para a seleção manual da bibliografia, identificação e exclusão do material duplicado, organização e revisão de títulos e resumos, além de gerenciamento das referências.

Os estudos foram triados para verificação dos critérios de elegibilidade sendo utilizados para a revisão sistemática quando atenderem aos critérios de exclusão e inclusão. A apresentação do processo de triagem dos estudos foi ilustrada pelo diagrama de fluxo PRISMA (20) (figura 1).

2.4 AVALIAÇÃO DO RISCO DE VIÉS

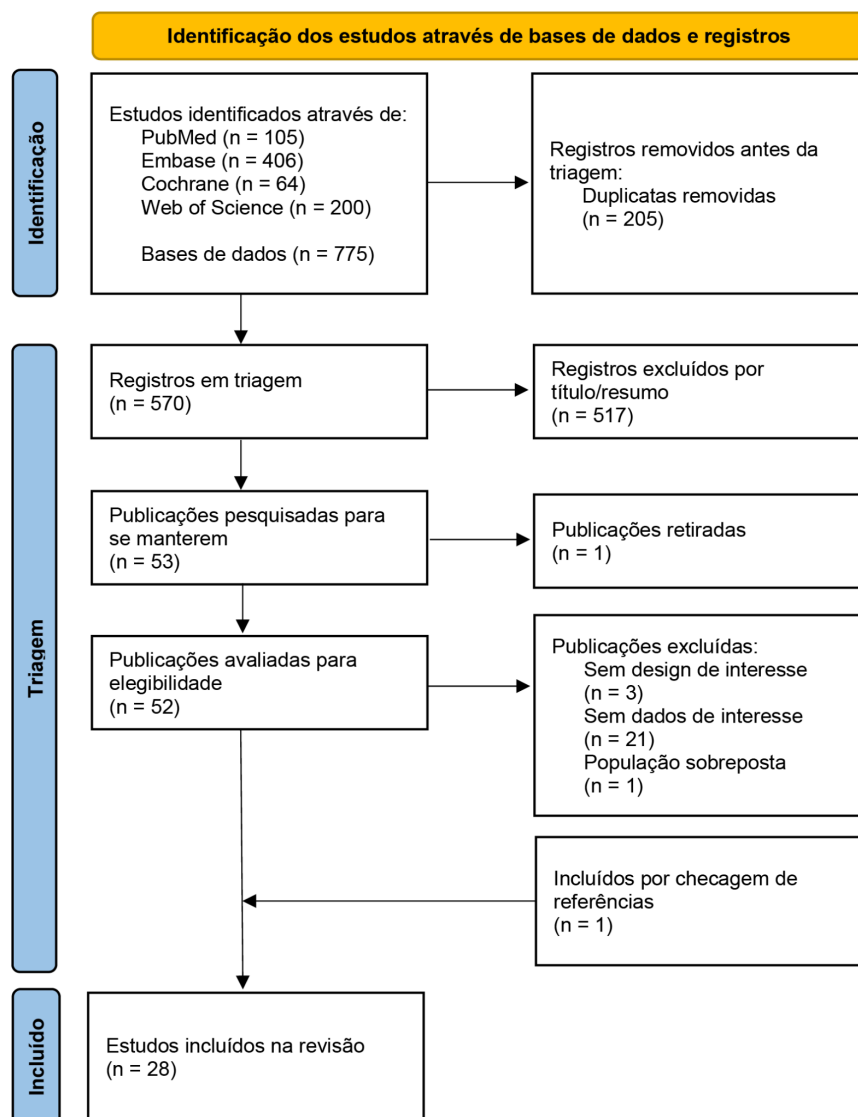
A avaliação do risco de viés foi realizada por meio da ferramenta ROBINS I (Risk of Bias In Non-Randomized studies of interventions) (21), que corresponderam aos estudos incluídos após a etapa de triagem. A ferramenta avalia o risco de viés em diferentes domínios, incluindo viés por confundimento, seleção de participantes, classificação das intervenções, dados ausentes, mensuração dos desfechos e seleção dos resultados relatados. Conforme os critérios ROBINS-I (21), os estudos foram classificados como apresentando baixo, moderado, sério ou crítico risco de viés. Por se tratar de uma avaliação baseada em julgamento por domínios, a ferramenta não utiliza pontuação numérica, sendo a classificação global do estudo determinada pelo domínio de maior risco.

3 RESULTADOS

3.1 SELEÇÃO DOS ESTUDOS

A busca nas quatro bases de dados identificou 775 referências, das quais 205 foram removidas por estarem duplicadas e 517 foram excluídas por título e resumo. Dessas referências apenas uma não possibilitou o acesso do texto na íntegra, sendo, portanto, excluída. Demais passaram para leitura do texto completo, e neste momento foram descartados três por não ter design de interesse, vinte e um por dados distintos dos buscados e um por população sobreposta. Além disso, um artigo foi incluído por checagem de referências. Assim, vinte e oito referências foram incluídas nesta revisão por atenderem a todos os critérios estabelecidos, conforme esquematizado pelo fluxograma PRISMA (20) presente na **Figura 1**.

Figura 1. Fluxograma PRISMA



Fonte: elaborado pelos autores

3.2 CARACTERÍSTICAS DOS ESTUDOS

Dos artigos selecionados, 15 eram coortes retrospectivas baseadas em revisão de prontuários, sete foram coortes prospectivas e seis eram séries de casos.

Cabe destacar que as séries de casos não constituíam, inicialmente, um critério obrigatório de inclusão. No entanto, estudos com esse delineamento também foram considerados elegíveis desde que incluíssem pelo menos um paciente com síndrome de SLG com idade inferior a 18 anos no momento do implante da ENV. Em alguns artigos, embora a amostra total fosse maior, o número específico de pacientes com SLG era reduzido. Ainda assim, esses estudos foram

mantidos na análise, sendo considerados exclusivamente os dados referentes a esses pacientes.

No conjunto dos estudos primários, foram incluídos um total de 456 indivíduos, com tamanho amostral variando de 1 a 146. A faixa etária no momento do implante da ENV variou de um mês de vida a 18 anos. A **Tabela 1** apresenta, para cada estudo, o delineamento, tamanho da amostra, idade no momento de inserção do eletrodo, tempo entre a cirurgia e o início do estímulo elétrico, os parâmetros iniciais de corrente e frequência, os tempos de estimulação e repouso (on/off), os desfechos primários e secundários, os eventos adversos e o tempo de seguimento de cada estudo.

Tabela 1. Dados gerais dos artigos selecionados

Autor, Ano	Design	Amostra	Idade de início das crises epiléticas (meses), média $\pm$ desvio padrão	Idade de inserção (meses), média $\pm$ desvio padrão	Tempo de ativação do eletrodo após cirurgia (em dias)	Corrente inicial do eletrodo (mA)	Frequência (Hz)	Tempo ON(s)//OFF(min)	Desfechos primários	Desfechos secundários	Efeitos adversos	Tempo de seguimento (meses)
Abdelmoity, 2021 (22)	CR	71	18	20,82	NA	NA	NA	NA	NC	SO, AT, AL	I, D, PR, MV, O	24
Alanazi, 2022 (23)	CR	4	18,8 $\pm$ 20,5	11,7 $\pm$ 3,3	7 - 15	0,25	NA	30//5	NC	NA	DI	48
Bremer, 2006 (24)	CR	11	NA	NA	NA	NA	NA	30//5	NC, QC	AL	Óbito	36
Buoni, 2004 (25)	SC	5	33 $\pm$ 39,4	199,2 $\pm$ 18,2	14	0,25	NA	25,4 $\pm$ 10,3 ; 3,25 $\pm$ 2,42	NC, QC	AL, CO	C	36
Cukiert, 2013 (26)	CP	14	NA	NA	21	0,25	30	30//5	QC	HM	R	NA
Cukiert, 2024 (27)	CR	19	NA	86,4	NA	NA	NA	NA	NC	NA	NA	48
Elliott, 2011 (28)	CR	11	NA	NA	NA	NA	NA	NA	NC	NA	NA	>3
Fang, 2020 (29)	CR	NA	NA	NA	NA	0,25	30	30//5	NC	NA	NA	24
Flesler, 2017 (30)	CR	88	NA	NA	14 a 21 dias	0,25	20-30	30//1,1-5	NC, QC	NA	NA	24
Frost, 2001 (31)	CR	50	NA	NA	NA	0,25	30	30//5	NC, QC	AL/AT, CO	I, D, R, T, PC, PR, S	6
Hallböök, 2005 (32)	CP	4	18 $\pm$ 28	NA	NA	0,25	30	30//5	NC, QC	NA	NA	9
Hentati, 2013 (33)	CR	3	NA	96	NA	NA	NA	30//5	NC	NA	NA	18 (média)

Hosain, 2000 (34)	SC	8	NA	142,5 ± 47,8	NA	0,75	NA	30//5	NC	NA	NA	6
Katagiri, 2016 (35)	CR	8	14,8 ± 13,15	87 ± 43,85	14 a 21	0,25	NA	30//5	NC	NA	R	60
Kruse, 2010 (36)	SC	1	60 ± 0	132 ± 0	NA	2,5	NA	30//5	NC, QC	CO	NA	43,2
Lagae, 2012 (37)	CR	20	NA	NA	NA	2	25	30//5	NC	NA	NA	>6
Lundgren, 1998 (38)	SC	3	5 ± 1	76 ± 30,2	1 a 5	0,25	30	30//5	NC	NA	S, A	18
Majoie, 2005 (39)	CP	12	23,33 ± 29,06	129,45 ± 38,1	1	0,25	NA	30//3	NC, QC	NA	NA	24
Mikati, 2009 (40)	CR	2	72 ± 16,97	174 ± 59,4	7 a 14	0,25	30	30//5	NC	CO	NA	27
Orosz, 2014 (41)	CR	146	NA	NA	NA	NA	NA	NA	NC	NA	NA	24
Parker, 1999 (42)	CP	9	12,4 ± 14,09	133,1 ± 37,8	NA	0,25	NA	30//6	NC	NA	I	24
Preto Mimura, 2017 (43)	SC	1	0 ± 0	120 ± 0	NA	NA	NA	NA	NC, QC	RM	NA	24
Rossignol, 2009 (44)	CP	5	27,2 ± 16,89	NA	NA	0,25	NA	NA	NC, QC	NA	DI, Óbito	24
Rychlicki, 2006 (45)	CP	9	NA	133,2 ± NA	NA	0,5	30	30//5	NC	NA	NA	36
Shahwan, 2009 (18)	CR	9	NA	126,72 ± 39,6	NA	0,25	30	30//3	NC, QC	NA	AP	102
Tekin, 2017 (46)	CP	3	48 ± 24	128 ± 38,6	NA	NA	NA	NA	NC, QC	NA	NA	34
Tormasiova, 2014 (47)	SC	1	NA	84 ± 0	0	0,25	20	30//3	NC	HM	NA	36
Zamponi, 2011 (48)	CR	10	NA	134,76 ± 41,37	NA	NA	NA	NA	NC, QC	NA	NA	12

Legenda: A - astenia, AL - Alerta, AP - Agitação psicomotora, AT - Atenção, C - Cefaleia, CO - Comunicação (Verbal e social), CP - Coorte prospectiva, CR - Coorte retrospectiva, D - DOR, DI - disfagia, HM - Honey moon, I - Infecção, MV - Mudança na voz, NA - Não disponível NC - Número de crise, O - Outro, PC - Parestesia cervical, PR - Problemas de respiração, QC - Qualidade das crises, R - Rouquidão, RM - redução de medicamentos, S - sialorreia, SC - Série de casos, SO - Sono, T - Tosse

Fonte: elaborado pelos autores

Quanto ao tempo de ativação do eletrodo após cirurgia, a maioria dos estudos não tinha essa informação disponível, mas quando existia ele variava de 7 a 21 dias, sendo acionado quando houvesse boa cicatrização, ausência de sinais infecciosos no local e conforme os protocolos específicos de cada estudo.

Os parâmetros de estimulação do nervo vago também seguiram as particularidades de cada centro. A corrente inicial de 0,25 mA foi a escolhida em 53,5% dos estudos selecionados, no entanto alguns centros optaram por início com 0,5 mA e 0,75 mA. Mesmo assim, houve um aumento na corrente elétrica utilizada

conforme diretriz de cada estudo ou ainda conforme tolerância individual dos pacientes. Já a frequência da onda utilizada nos trabalhos em que este dado foi registrado, variaram de 20 a 30 Hz, progredindo ou não conforme tolerância do paciente e protocolos individuais dos centros.

O tempo on-off corresponde ao tempo cíclico em que o estímulo ao vago acontece seguido do tempo em que ele desliga, portanto não acontece. O tempo de 30 segundos de estimulação foi utilizado em 67,8% dos estudos selecionados sendo quase unanimidade quando este dado foi reportado. Já o tempo off variou em um intervalo de 2 a aproximadamente 10 minutos, não havendo um consenso de qual seria o ideal.

O tempo de seguimento também foi uma variável particular, compreendendo um intervalo de 3 a 102 meses.

3.3 AVALIAÇÃO DO RISCO DE VIÉS DOS ESTUDOS

Todos os estudos incluídos nesta revisão apresentaram delineamento observacional e foram avaliados por meio da ferramenta ROBINS-I. O estudo de Alanazi et al. (23) foi o único a incorporar grupo comparador entre a ENV e outra intervenção, sendo classificado com risco de viés crítico, principalmente em decorrência de limitações no domínio de confundimento (D1).

Em relação à classificação global, 5 dos 28 estudos foram categorizados como apresentando risco de viés crítico — Abdelmoity et al. (22), Alanazi et al. (23), Bremer et al. (24), Fang et al. (29) e Kruse et al. (36). Os demais 23 estudos foram classificados com risco de viés sério, não sendo identificado nenhum estudo com risco de viés baixo ou moderado. A distribuição detalhada do risco de viés por domínios, bem como a avaliação individual de cada estudo, encontra-se apresentada na **Figura 2**.

Figura 2. Risco de Viés



3.4 DESFECHOS PRIMÁRIOS

Dois parâmetros foram considerados como desfecho primário: o número de crises epiléticas e a qualidade das crises apresentadas após intervenção. A grande maioria dos artigos (96,4%) trouxe em seus resultados o número de crises, no entanto apenas 42,8% apresentou o tipo de crise pós ENV.

3.4.1 VARIAÇÃO DO NÚMERO DE CRISES APÓS A ENV

3.4.1.1 VISÃO GERAL DA AMOSTRA E CATEGORIZAÇÃO DA RESPOSTA

A análise da efetividade da Estimulação do Nervo Vago (ENV) na redução da frequência de crises epiléticas evidenciou acentuada heterogeneidade metodológica entre os estudos incluídos. Para mitigar essa variabilidade e permitir maior comparabilidade entre os achados, os desfechos foram estratificados conforme o tempo de seguimento pós-implante, abrangendo avaliações precoces (1 – 6 meses), intermediárias e de longo prazo (>24 meses). Os estudos que apresentaram tempos de seguimento capazes de serem padronizados foram sistematizados na **Tabela 2**.

A resposta ao tratamento foi majoritariamente definida com base na proporção de pacientes que alcançaram reduções $\geq 50\%$ ou $\geq 75\%$ na frequência de crises, complementada pela identificação de pacientes livres de crises, daqueles em que não foi observada alteração, e os que observaram piora clínica.

Estudos que empregaram métricas globais de resposta ou que não apresentaram padronização do tempo de seguimento foram agrupados em uma categoria analítica específica, sendo seus resultados sintetizados de forma descritiva quanto às tendências gerais de efetividade.

Tabela 2 - Resultados relativos ao número de crises de todas as modalidades após a ENV

Autor, Ano	Amostra	Aumento do número de crises, n (%)	Manutenção do número de crises, n (%)	Diminuição <50% no número de crises, n (%)	Diminuição >50% no número de crises, n (%)	Diminuição >75% no número de crises, n (%)	Livre de crises
1 mês após ENV							
Abdelmoity, 2021 (22)	26	4 (15%)	7 (27%)	5 (19%)	4 (15%)	3 (12%)	3 (12%)
Frost, 2001 (31)	46	1 (2%)	-	-	20 (43%)	7 (15%)	-
3 meses após a ENV							
Abdelmoity, 2021 (22)	32	4 (13%)	10 (31%)	4 (13%)	8 (25%)	3 (9%)	3 (9%)
Frost, 2001 (31)	43	3 (7%)	-	-	24 (56%)	15 (35%)	-
6 meses após a ENV							
Abdelmoity, 2021 (22)	44	3 (7%)	9 (21%)	8 (18%)	8 (18%)	11 (25%)	5 (11%)
Frost, 2001 (31)	24	-	-	-	14 (58%)	9 (37%)	-
Hosain, 2000 (34)	8	-	1 (12,5%)	3 (37,5%)	1 (12,5%)	3 (37,5%)	-
Orosz, 2014 (41)	123	-	-	-	35 (28%)	-	-
Rossignol, 2009 (44)	5	-	2 (40%)	-	-	3 (60%)	-
9 meses após a ENV							
Hallböök, 2005 (32)	4	1 (25%)	1 (25%)	1 (25%)	1 (25%)	-	-
12 meses após ENV							
Abdelmoity, 2021 (22)	37	6 (16%)	2 (5%)	4 (11%)	12 (32%)	9 (30%)	4 (11%)
Katagiri, 2016 (35)	8	-	2 (25%)	1 (12,5%)	1 (12,5%)	2 (25%)	2 (25%)
Mikati, 2009 (40)	1	-	-	1 (100%)	-	-	-
Orosz, 2014 (41)	146	-	-	-	48 (33%)	-	-

3.4.1.2 RESULTADOS A CURTO PRAZO (1 A 6 MESES PÓS ENV)

Nos primeiros meses após a implantação do dispositivo, observou-se elevada variabilidade na resposta terapêutica entre os estudos, refletindo diferenças nas características das amostras e nos delineamentos metodológicos. No primeiro mês de seguimento, a coorte de Abdelmoity et al. (22) demonstrou resposta ainda incipiente, com 27% dos pacientes sem alteração na frequência de crises e 15% apresentando piora clínica. Ainda assim, uma parcela já evidenciava benefício precoce, com 12% alcançando redução >50% e outros 12% >75%. Em contraste, Frost et al. (31) reportaram uma resposta inicial mais expressiva, com 43% dos pacientes atingindo redução >50% já nesse período.

Aos três meses, observa-se, de modo geral, uma tendência de incremento na efetividade. No estudo de Frost et al. (31), a proporção de respondedores aumentou para 56% com redução >50% e 35% com redução >75%, indicando progressão do efeito terapêutico ao longo do tempo. Por outro lado, em Rychlicki et al. (45) observou-se uma redução média global de apenas 8% na frequência de crises no mesmo intervalo, evidenciando que a magnitude da resposta inicial pode permanecer limitada em determinadas coortes.

Ao atingir seis meses de seguimento, os efeitos da neuromodulação tornam-se mais consistentes na maioria dos estudos. Frost et al. (31) manteve taxas elevadas de resposta, com 58% dos pacientes apresentando redução >50% e 37% >75%. Na coorte de maior dimensão, Orosz et al. (41), 28% dos pacientes alcançaram redução >50%. De forma semelhante, Fang et al. (29), ao avaliar especificamente pacientes com Síndrome de Lennox–Gastaut, observou redução média de 73,1% na frequência de crises aos 24 meses. Resultados de menor magnitude foram descritos por Parker et al. (42), no qual, no intervalo de 0 a 6 meses, 55% dos pacientes permaneceram com redução <50%, embora 33% já apresentassem resposta >50%, havendo um caso de piora clínica.

Casos isolados de resposta precoce marcante também foram descritos, como no estudo de Tormasiova et al. (47), que relatou um paciente livre de crises já no quarto mês pós-implante; entretanto, esse desfecho não se manteve em avaliações subsequentes. Em conjunto, esses achados sugerem que, embora benefícios clínicos possam ser observados precocemente, a resposta à estimulação do nervo

vago tende a se intensificar progressivamente ao longo dos primeiros meses após a implantação, com considerável heterogeneidade entre os estudos.

3.4.1.3 RESULTADOS A MÉDIO PRAZO (9 A 12 MESES PÓS-ENV)

No acompanhamento de médio prazo, os índices de controle de crises tenderam a se manter ou a apresentar trajetória ascendente na maioria dos estudos. Aos 12 meses, Orosz et al. (41) relataram que 33% dos pacientes atingiram redução >50% na frequência de crises. De forma consistente, Abdelmoity et al. (22) observaram resultados expressivos nesse mesmo marco temporal, com 32% dos pacientes alcançando redução >50%, 30% >75% e 11% tornando-se livres de crises.

A evolução favorável ao longo do primeiro ano também foi descrita por Parker et al. (42). No intervalo de 6 a 12 meses, a proporção de respondedores ($\geq 50\%$) aumentou para 5/9 pacientes, incluindo um caso de resposta excelente ($\geq 90\%$). Entretanto, observou-se concomitantemente aumento na proporção de pacientes com piora clínica (3/9), evidenciando a variabilidade interindividual da resposta. De maneira semelhante, em Rychlicki et al. (45) demonstrou-se progressão gradual da efetividade, com a redução média da frequência de crises aumentando de 3% no sexto mês para 33% ao final de 12 meses.

Em contraste com essa tendência predominantemente positiva, Lundgren et al (38) identificaram ausência de ganho clínico significativo no período de 10 a 12 meses, em uma amostra reduzida ($n=3$), na qual nenhum paciente ultrapassou 80% de redução e predominou a estabilidade clínica (2/3). Conjuntamente, os resultados sugerem que a efetividade da intervenção tende a se consolidar ao longo do primeiro ano, embora com variabilidade substancial entre os estudos, incluindo a presença de subgrupos com resposta limitada, ausência de benefício clínico mensurável ou mesmo piora das crises.

3.4.1.4 RESULTADOS A LONGO PRAZO (>12 A ≥ 24 MESES PÓS-ENV)

A análise de seguimentos superiores a 12 meses reforça o caráter progressivo e cumulativo da efetividade da ENV entre os pacientes respondedores. Nesse intervalo, Cukiert et al. (27) e Lagae et al. (37) reportaram proporções elevadas de resposta clínica, com 79% e 60% das respectivas amostras atingindo

redução >50% na frequência de crises. Adicionalmente, Bremer et al. (24) descreveram um achado clinicamente relevante, no qual 27% dos pacientes evoluíram livres especificamente de crises atônicas, sugerindo um efeito potencialmente diferenciado da ENV sobre subtipos de crises de maior impacto funcional.

Por volta de 18 meses de seguimento, Abdelmoity et al. (22) evidenciaram predomínio de respostas robustas, com 42% dos pacientes apresentando redução >75% e 21% atingindo remissão completa das crises. Em consonância, os dados longitudinais de Rychlicki et al. (45) demonstraram manutenção e progressão da efetividade ao longo do tempo, com redução média da frequência de crises de 45% em 18 meses, atingindo 50% em 24 meses, seguida de discreta redução para 31% após três anos de acompanhamento.

Nos estudos com seguimento igual ou superior a 24 meses, observa-se consolidação do benefício terapêutico em parte significativa das coortes. Flesler et al. (30) reportaram uma das maiores taxas de resposta, com 81% dos pacientes alcançando redução >50%. Resultados mais moderados foram descritos por Orosz et al. (41), com 39% dos indivíduos nessa mesma faixa de resposta. Abdelmoity et al. (22) demonstraram manutenção de respostas expressivas em longo prazo, com 30% dos pacientes apresentando redução >75% e 17% permanecendo livres de crises.

Apesar desses achados favoráveis, alguns estudos apontam para a possibilidade de perda de efetividade ao longo do tempo. Nesse contexto, Tormasiova et al. (47) descreveram um caso de resposta inicial completa que não se sustentou, com retorno dos níveis de frequência de crises ao basal após três anos de seguimento, sugerindo a ocorrência potencial de tolerância ou atenuação do efeito terapêutico em casos isolados.

3.4.1.5 DESFECHOS VARIÁVEIS E ACHADOS INDEPENDENTES

Para além das análises estratificadas por tempo de seguimento, parte dos estudos reportou seus resultados por meio de métricas globais de resposta ou com ênfase em desfechos desfavoráveis, o que amplia a compreensão do espectro de efeitos da intervenção. Nesse contexto, foi observado por Elliott et al. (28), uma redução global de 51%, enquanto Hentati et al. (33) reportaram uma mediana de

redução mais modesta (23%), evidenciando a variabilidade de magnitude entre diferentes amostras. Em nível individual, Preto Mimura et al. (43) documentaram um caso com resposta clínica marcante, caracterizado por redução absoluta da frequência de crises de sete para duas ocorrências diárias.

Em contraposição, os dados também evidenciam a ocorrência não desprezível de ausência de resposta ou mesmo de desfechos adversos. Cukiert et al. (26) relataram agravamento das crises em 5 de 14 pacientes, correspondendo a uma proporção relevante de não respondedores com piora clínica. De forma semelhante, Majoie et al. (39), em uma amostra de 12 indivíduos, observaram que 8 não atingiram o limiar de redução >50%, incluindo dois casos de aumento na frequência de crises e um sem alteração em relação ao basal. Ademais, o seguimento tardio descrito por Lundgren et al. (38) (16–18 meses) reforça essa heterogeneidade de resposta, com distribuição equitativa entre piora clínica e estabilidade (50% cada), sem registro de melhora significativa nesse intervalo.

Considerando o conjunto dos estudos, esses achados indicam que, embora a ENV demonstre benefício clínico global em parcela substancial dos pacientes, a resposta terapêutica não é uniforme, sendo observadas tanto variações na magnitude do efeito quanto a presença de subgrupos com resposta limitada ou evolução desfavorável.

3.4.2 RESPOSTA POR TIPO E QUALIDADE DAS CRISES

Para a análise dos desfechos relacionados à qualidade e ao tipo das crises, os dados foram organizados segundo categorias semiológicas, permitindo avaliar de forma mais refinada a resposta à ENV entre diferentes subtipos de crises, bem como em aspectos qualitativos, como intensidade e duração dos eventos.

3.4.2.1 CRISES ATÔNICAS E DE QUEDA (DROP ATTACKS - DA)

As crises atônicas e de queda demonstraram, de modo geral, elevada responsividade à ENV, embora com variabilidade entre as coortes. Bremer et al. (24) observaram resolução completa (100%) desse subtipo em 3 pacientes (27%), enquanto Buoni et al. (25) reportaram redução de 50% em dois pacientes e remissão

completa em um caso. Em uma amostra mais robusta, Flesler et al. (30), composta por pacientes com SLG, documentaram redução média de 82% nas crises atônicas de queda.

Dados longitudinais de Frost et al. (31) evidenciam um padrão de resposta progressiva, com reduções medianas de 47% no primeiro mês, 55% no terceiro mês e 88% no sexto mês pós-implante. De forma semelhante, Shahwan et al. (18) descreveram abolição das crises atônicas diurnas em 5 de 7 pacientes, sem recorrência desse subtipo ao final do seguimento em indivíduos com SLG. Resultados adicionais incluem redução de 52,6% em um paciente no estudo de Hallböök et al. (32) e remissão completa após dois anos no relato de Rossignol et al. (44). Em contrapartida, Cukiert et al. (26) não identificaram melhora estatisticamente significativa para crises atônicas em sua amostra, ressaltando a heterogeneidade dos resultados.

3.4.2.2 CRISES TÔNICAS E TÔNICO-CLÔNICAS GENERALIZADAS

A resposta das crises tônicas e tônico-clônicas generalizadas foi, em geral, favorável, com reduções substanciais descritas em diferentes estudos. Flesler et al. (30) reportaram redução de 96% nas crises tônicas em pacientes com SLG, enquanto Kruse et al. (36) e Cukiert et al. (26) documentaram diminuição na frequência de crises tônicas e tônico-clônicas generalizadas.

Shahwan et al. (18) observou a abolição completa das crises tônicas no período diurno, com persistência apenas de eventos noturnos ou ao despertar. Rossignol et al. (44) relataram redução superior a 50% em dois pacientes ao longo de dois anos, e Tekin et al. (46) descreveram redução de crises tônicas generalizadas com queda cefálica em um caso. Por outro lado, Cukiert et al. (26) também relataram ausência de melhora significativa nesse subtipo em parte de sua coorte, indicando variabilidade na resposta.

3.4.2.3 CRISES DE AUSÊNCIA E MIOCLÔNICAS

Para crises de ausência e mioclônicas, os achados sugerem resposta consistente, frequentemente com padrão de melhora progressiva. Frost et al. (31)

demonstraram redução mediana das ausências atípicas de 48% no primeiro mês, 73% no terceiro mês e 81% no sexto mês. Flesler et al. (30) reportaram redução de 73% nas crises de ausência, enquanto Cukiert et al. (26) descreveram efetividade da ENV tanto para crises de ausência atípica quanto para crises mioclônicas.

Hallböök et al. (32) documentaram cessação completa das crises mioclônicas em um paciente; contudo, observou-se heterogeneidade intra coorte, com outro indivíduo apresentando redução de 55,5% nas ausências atípicas, porém aumento de 100% nas crises secundariamente generalizadas. Achados adicionais de Rossignol et al. e Tekin et al. (46) incluem casos de remissão completa ou redução relevante em crises mioclônicas e de ausência mioclônica.

3.4.2.4 OUTROS SUBTIPOS E ASPECTOS QUALITATIVOS DAS CRISES

Em relação a outros subtipos, Frost et al. (31) reportou reduções mais modestas em crises parciais complexas, com diminuições de 20% no primeiro mês e 23% no terceiro mês. Hallböök et al. (32) descreveram redução sustentada de 50% em crises secundariamente generalizadas em um paciente após nove meses, contrastando com aumento de 33,3% em outro indivíduo. Majoie et al. (39), por sua vez, destacaram que, embora diferentes subtipos apresentem respostas nominais distintas, tais diferenças não atingiram significância estatística.

Quanto aos desfechos qualitativos, os dados sugerem impacto adicional da ENV além da frequência de crises. Preto Mimura et al. (43) relataram redução na intensidade e duração dos eventos, enquanto Shahwan et al. (18) descreveram crises mais leves, de menor duração e associadas a recuperação pós-ictal mais rápida. Esses achados indicam que os benefícios da ENV podem se estender à modulação da gravidade clínica das crises, mesmo em casos com redução quantitativa limitada.

3.5 DESFECHOS SECUNDÁRIOS

A análise dos desfechos secundários revelou uma significativa heterogeneidade metodológica, apresentando-se como variáveis abstratas devido à falta de padronização entre as referências selecionadas. Cada estudo adotou

critérios distintos de avaliação, frequentemente baseados em escalas não validadas ou na percepção subjetiva dos cuidadores, o que limita a uniformidade dos dados.

Apesar dessa variação, observou-se uma melhora em diferentes aspectos na qualidade de vida dos pacientes, manifestada principalmente por incrementos no estado de alerta, atenção, padrão de sono e nas habilidades de comunicação verbal e social. Notou-se também o fenômeno de *honeymoon* (HM) e a redução da carga farmacológica diária em alguns casos.

3.5.1 ESTADO DE ALERTA, ATENÇÃO E SONO

Alterações no estado de alerta foram reportadas de forma longitudinal em diferentes estudos, com variação ao longo do seguimento. Abdelmoity et al. (22) documentaram a melhora do alerta em 7/26 pacientes no primeiro mês, 8/32 no terceiro mês, 22/44 no sexto mês, 12/37 aos 12 meses, 14/24 aos 18 meses e 12/23 aos 24 meses pós-implante. De maneira consistente, Frost et al. (31) observaram melhora em mais de 60% dos pacientes aos 3 meses e em mais de 50% aos 6 meses. Bremer et al. (24) registraram aumento do estado de alerta em 6/11 pacientes, com início médio dos efeitos em aproximadamente 2,5 meses, enquanto Buoni et al. reportaram esse achado em 1/5 pacientes.

Resultados semelhantes foram observados no domínio da atenção. Abdelmoity et al. (22) identificaram melhora em 7/26 pacientes no primeiro mês, 8/32 no terceiro mês, 22/44 no sexto mês, 11/37 aos 12 meses, 14/24 aos 18 meses e 12/23 aos 24 meses, sugerindo comportamento temporal comparável ao observado para o estado de alerta.

No que se refere ao sono, Abdelmoity et al. (22) também reportaram variações ao longo do tempo, com melhora em 5 pacientes no primeiro mês, 9 no terceiro mês, 19 no sexto mês, 11 aos 12 meses, 13 aos 18 meses e 11 aos 24 meses, evidenciando coexistência de respostas positivas e ausência de efeito em subgrupos ao longo do seguimento.

3.5.2 COMUNICAÇÃO, COMPORTAMENTO E DESEMPENHO ESCOLAR

Mudanças nos domínios de comunicação e interação social foram descritas em múltiplas coortes, ainda que de forma menos padronizada. Frost et al. (31)

relataram que, após 6 meses de tratamento, pelo menos 25% dos pacientes apresentaram alterações na comunicação verbal e no desempenho escolar. Buoni et al. (25) observaram aumento da comunicação social em 20% dos pacientes, enquanto Mikati et al. (40) registraram melhora em aspectos sociais em dois indivíduos. De forma pontual, Kruse et al. (36) também descreveram melhora na comunicação em um paciente.

No domínio comportamental, Preto Mimura et al. (43) relataram melhora global do comportamento. Alterações adicionais incluíram aumento do apetite, observado por Buoni et al. (25) em 20% dos pacientes.

3.5.3 PARÂMETROS CLÍNICOS E TERAPÊUTICOS ADICIONAIS

Entre os fenômenos clínicos observados, destaca-se o denominado “*honeymoon*”, caracterizado por redução transitória da frequência de crises antes da ativação do dispositivo ou imediatamente após o implante. Esse padrão foi descrito por Cukiert et al. (26) em aproximadamente 85% dos pacientes, bem como por Tormasiova et al. (47).

Adicionalmente, Frost et al. (31) reportaram melhora na recuperação pós-ictal e redução no agrupamento de crises em pelo menos 25% dos pacientes após seis meses de seguimento. No âmbito do manejo terapêutico, Preto Mimura et al. (43) descreveram redução no número de fármacos antiepilépticos utilizados, sugerindo potencial impacto da ENV na otimização do tratamento farmacológico.

De forma global, os desfechos secundários indicam que os efeitos da ENV podem se estender além da frequência de crises, envolvendo múltiplos domínios funcionais. Contudo, observa-se variabilidade entre os estudos quanto à magnitude e consistência desses achados, bem como limitações relacionadas à heterogeneidade metodológica e à ausência de padronização nas medidas utilizadas.

3.6 EFEITOS ADVERSOS

3.6.1. ALTERAÇÕES DE VOZ E SINTOMAS RESPIRATÓRIOS

Eventos relacionados à fonação e ao trato respiratório foram os mais frequentemente descritos entre os estudos incluídos. Frost et al. (31) relataram alteração da voz ou rouquidão em 22/50 pacientes, além de tosse em 15/50 casos. Achados semelhantes foram observados por Katagiri et al. (35), com rouquidão em 2/8 pacientes, e por Cukiert et al. (26), em 1/14 indivíduos.

No período pós-operatório precoce, Abdelmoity et al. (22) identificaram a ocorrência de efeitos adversos em 10/26 pacientes no primeiro mês, incluindo alterações vocais e sintomas respiratórios. Episódios de dispneia também foram reportados por Frost et al. (31), ainda que em menor proporção. De modo geral, os estudos indicam que esses eventos tendem a apresentar caráter transitório, com resolução espontânea ao longo do tempo ou após ajustes nos parâmetros de estimulação.

3.6.2 COMPLICAÇÕES NO SÍTIO CIRÚRGICO E INFECÇÕES

Complicações locais relacionadas ao procedimento cirúrgico foram descritas em diferentes frequências. Abdelmoity et al. (22) relataram casos de infecção recorrente no sítio de implantação. Frost et al. (31) registraram dor local em aproximadamente 10% dos pacientes e infecção em 4% da amostra. Em situações pontuais, eventos infecciosos implicaram intervenções adicionais, como a remoção do dispositivo, conforme descrito por Parker et al. (42) em um paciente.

3.6.3 DISFAGIA, SIALORREIA E OUTROS EVENTOS SISTÊMICOS

Eventos adversos envolvendo deglutição e manifestações sistêmicas também foram reportados, embora com menor frequência. Alanazi et al. (23) descreveram disfagia em 1/4 pacientes, enquanto Rossignol et al. (44) relataram um caso de disfagia grave que levou à retirada do dispositivo. Lundgren et al. (38) observaram aumento da salivação em 1/3 pacientes.

Outros eventos incluíram cefaleia associada ao aumento da intensidade de estimulação, descrita por Buoni et al. (25) em um paciente (1,25 mA), além de fadiga intensa em 2/3 indivíduos no estudo de Lundgren et al. (38). Alterações comportamentais foram reportadas por Shahwan et al. (18) em 2/9 pacientes, e parestesia cervical foi descrita por Frost et al. (31). Esses achados refletem a

diversidade de manifestações sistêmicas associadas à terapia, geralmente descritas de forma isolada e em pequenas proporções.

3.6.4. ÓBITOS REGISTRADOS

Durante o seguimento dos estudos incluídos, foram registrados dois óbitos. Bremer et al. (24) reportaram um caso de morte súbita oito meses após o implante, sem atribuição causal ao dispositivo de ENV. Rossignol et al. (44) descreveram um óbito decorrente de obstrução de vias aéreas durante alimentação, também sem relação direta estabelecida com a intervenção.

4 DISCUSSÃO

A análise dos dados evidencia que a Estimulação do Nervo Vago (ENV) promove uma resposta terapêutica de caráter progressivo, na qual a redução da frequência de crises tende a se consolidar e a se intensificar ao longo do primeiro ano de seguimento. Tal observação é ratificada pela *American Academy of Neurology* (AAN) com nível de evidência C (49). Enquanto os meses iniciais apresentam respostas heterogêneas, os períodos de acompanhamento mais extensos revelam taxas de efetividade mais robustas, incluindo, em casos específicos, a remissão completa (18,22,24,35,44). Entretanto, como a resposta não é unânime, depreende-se que a efetividade da neuromodulação seja determinada tanto por características intrínsecas de cada paciente quanto pelo delineamento metodológico dos estudos.

Além da dimensão quantitativa, a ENV demonstra efetividade variável conforme a semiologia das crises, com benefícios particularmente expressivos nas atônicas (18,24,25,30,31,32,44), além de resultados consistentes nas tônicas (18,26,30,32,36,44,46) e de ausência (26,30,31,32,44,46). O impacto da intervenção transcende o controle numérico, refletindo-se na redução da gravidade e da duração dos eventos, bem como na melhora de desfechos secundários elementares, tais como o estado de alerta, a atenção e a qualidade do sono.

4.1 QUANTO À EFETIVIDADE: UMA AVALIAÇÃO DE NÚMERO E QUALIDADE DAS CRISES

A análise dos artigos desta revisão permitiu observar que a resposta geral na redução de crises epiléticas em pacientes com SLG foi positiva. Da amostra total de 456 pacientes, 30 apresentaram aumento no número de crises, 46 demonstraram resposta indiferente e 375 indicaram melhora clínica de, pelo menos, 50% na redução dos episódios. Desses respondedores 28 crianças ficaram livres de todos os tipos de crise convulsiva. Adicionalmente, registraram-se dois óbitos e três remoções de dispositivos, as quais serão detalhadas oportunamente.

Sob a ótica individual dos artigos revisados, o estudo com a maior amostra (41) indicou que o impacto da intervenção varia conforme o tipo de crise epilética predominante no paciente. Observou-se, nesse trabalho, que embora a redução na

frequência das crises não tenha sido tão expressiva, a maior parte da amostra apresentava convulsões do tipo tônico-clônica generalizada. Tal dado corrobora a premissa de que os melhores respondedores na SLG são pacientes cujas sintomatologias predominantes envolvem crises de queda (*drop attacks*) (30,31).

No trabalho de Frost et al. (31), as crises atônicas (*drop attacks*) apresentaram redução expressiva após a Estimulação do Nervo Vago (ENV), resultado semelhante ao descrito em outros estudos da literatura (50,9). Esse achado evidencia a relevância da intervenção, dado que crianças com essa condição sofrem crises severas a ponto de necessitarem do uso de capacetes para evitar traumatismos cranianos (51).

O conjunto dos estudos permitiu verificar que os pacientes mais beneficiados pela intervenção foram aqueles que sofriam com crises do tipo atônicas, tônicas e de ausência; estas duas últimas foram evidenciadas nos estudos de Flesler et al. (30), Frost et al. (31), Cukiert et al. (26), Kruse et al. (36), Halbook et al. (32), Rossignol et al. (44) e Tekin et al. (46).

Ressalta-se que, na amostra completa desta revisão (n=456), nem todos os pacientes apresentavam o mesmo quadro clínico inicial. As medicações utilizadas para o controle da SLG divergiam, assim como as comorbidades associadas, a idade e as cirurgias prévias. No estudo de Cukiert et al. (26), pacientes previamente submetidos à calosotomia ou à ressecção cortical responderam satisfatoriamente à ENV, demonstrando que técnicas neuromoduladoras podem ser aplicadas em indivíduos submetidos a procedimentos cirúrgicos convencionais. Esses achados são reforçados por Katagiri et al. (35).

Essa assimetria clínica inicial pode explicar a heterogeneidade das respostas à ENV. Além disso, tal variação associa-se ao fato de os estudos utilizarem diferentes eletrodos, bem como padrões de estimulação distintos entre si.

Nesse sentido, a *American Academy of Neurology* (AAN) recomenda que os parâmetros de estimulação inicial sigam os protocolos de seu *guideline* (51). Tais parâmetros estabelecem: corrente de saída de 0,25 mA, frequência de sinal de 30 Hz, largura de pulso de 250-500 μ s, tempo "on" de 30 segundos e tempo "off" de 300 segundos (5 minutos), com a corrente usualmente elevada para 2-3 mA, conforme a tolerância. Observa-se que, algumas referências bibliográficas utilizadas na confecção do referido *guideline* coincidem com os trabalhos revisados neste estudo.

4.2 QUANTO AOS DESFECHOS SECUNDÁRIOS

Conforme descrito anteriormente os desfechos secundários foram avaliados subjetivamente e são, portanto, enviesados.

O parâmetro de atenção e alerta configurou-se como um dos mais relevantes entre os desfechos secundários. Tal relevância decorre do fato de que indivíduos com SLG tem comprometimento de atenção e alerta porque convivem com descargas epileptiformes interictais persistentes que interrompem redes cognitivas (52), desorganização das redes cerebrais funcionais (53), e episódios de status epilepticus não-convulsivo (6).

Outra variável de desfecho secundário foi o aprimoramento da comunicação verbal e social. Ela é afetada em pacientes com SLG devido a mecanismos de deterioração cognitiva progressiva que afeta 75 a 95% dos pacientes, atividade epileptiforme persistente que interfere com redes corticais responsáveis pela linguagem e processamento social, lesões cerebrais estruturais subjacentes e efeitos adversos cognitivos de medicações antiepilépticas (2,6,54,55).

O conceito de *honeymoon* (HM) apareceu também como consequência do ENV em dois trabalhos analisados. Este período de HM é caracterizado por proporcionar alívio temporário das crises com melhora da qualidade de vida e função cognitiva, porém pode criar expectativas que podem não se sustentar a longo prazo (6).

Além disso, a redução de medicamentos pode ser também um dos desfechos secundários de interesse para os pacientes. Dentre os artigos revisados apenas Preto Mimura et al. (43), trouxe a avaliação deste ponto, o que aponta para o fato de que nem todos os estudos tiveram a preocupação de verificar todas as variáveis que acompanham o pós operatório de ENV para pacientes com SLG.

4.3 QUANTO AOS EFEITOS ADVERSOS DA ESTIMULAÇÃO DO NERVO VAGO

Os efeitos adversos da Estimulação do Nervo Vago (ENV) foram avaliados de modo assimétrico entre os estudos revisados. Os eventos de maior incidência relatados compreenderam: infecção pós-operatória, dor no local cirúrgico, problemas respiratórios e disfagia. Os dois primeiros eram previstos, uma vez que constituem

riscos inerentes a qualquer procedimento cirúrgico. No trabalho de Parker et al. (42), relatou-se a remoção de um dos dispositivos devido a complicações infecciosas.

A disfagia e os transtornos respiratórios após a implantação da ENV decorrem de dois mecanismos fisiopatológicos: a lesão cirúrgica direta do nervo vago e a estimulação elétrica das fibras eferentes laríngeas. Ambos os mecanismos convergem para a disfunção das pregas vocais e o comprometimento das vias aéreas (50,56). Pela mesma fundamentação anatômica, a alteração vocal e a rouquidão também se apresentam como efeitos adversos esperados.

O estudo de Rossignol et al. (44) indicou dois pontos relevantes quanto aos efeitos adversos: o primeiro refere-se ao paciente número 8, cuja disfagia severa culminou na remoção do dispositivo; o segundo concerne ao paciente número 6, que foi a óbito em decorrência de obstrução das vias aéreas durante a alimentação, fatalidade esta que não foi claramente atribuída à ENV. Além desse registro, um óbito foi relatado por Bremer et al. (24), envolvendo uma criança vítima de morte súbita de etiologia desconhecida, sendo o evento considerado uma consequência da epilepsia, e não um efeito colateral da estimulação.

Por fim, o artigo de Buoni et al. (25) foi o único a relatar cefaleia intratável pós-ENV, observada no paciente número 2. O quadro agravou-se com o aumento da corrente elétrica para 1,25 mA, seguido pelo incremento na frequência e na intensidade das crises. Houve a redução da corrente dez dias após o início do quadro e, posteriormente, a remoção do gerador a pedido do paciente por ineficácia. O mecanismo dessa cefaleia intensa decorre, provavelmente, da ativação do sistema trigeminovagal — área de conexões anatômicas extensas no tronco encefálico — gerando ativação nociceptiva do nervo em repouso (57).

4.4 LIMITAÇÕES E EXPECTATIVAS

A principal limitação deste trabalho reside na utilização de estudos de coorte retrospectivos. Tais estudos são considerados evidências de menor qualidade em comparação aos ensaios clínicos randomizados (ECRs), primordialmente pela ausência de randomização, o que os torna vulneráveis a vieses sistemáticos que podem distorcer as estimativas de efeito de uma intervenção. Essa fragilidade metodológica refletiu-se no fato de todos os artigos analisados apresentarem risco sério ou crítico de viés.

Ademais, o tamanho das amostras mostrou-se, em sua maioria, reduzido. Embora a SLG seja uma síndrome rara — o que justifica um número de participantes (n) geralmente menor — as bibliografias utilizadas carecem de amostras com significância estatística específica para a síndrome. Tal escassez reforça a compreensão de que a execução de ECR sobre este tema seja mais complexa. Ainda quanto à amostragem, a ocorrência de óbitos e a perda de seguimento de pacientes configuraram pontos de atenção, pois tornaram a amostra variável ao longo do tempo.

A ausência de padronização entre os artigos quanto ao tempo de seguimento, aos parâmetros de estimulação do eletrodo, às condições clínicas prévias, à idade e à definição dos desfechos também se apresentou como um limitador importante, visto que a busca por resultados uniformes partiu de cenários clínicos distintos.

Além do exposto, uma limitação central desta revisão refere-se ao elevado risco de viés no Domínio 5 do instrumento ROBINS-I (viés na mensuração dos desfechos), classificado como sério ou crítico em 100% dos estudos incluídos. A consistência desse achado sugere a presença de limitações estruturais inerentes aos estudos que avaliam a ENV no contexto da SLG, extrapolando falhas metodológicas pontuais. Entre os principais determinantes desse viés, destaca-se a inviabilidade prática do cegamento. Por se tratar de uma intervenção cirúrgica com implante de dispositivo, frequentemente associada a sinais físicos perceptíveis, os estudos assumem, em sua maioria, um delineamento aberto. Essa característica expõe a avaliação dos desfechos ao viés de aferição, uma vez que participantes, cuidadores e avaliadores detêm o conhecimento da intervenção realizada.

Adicionalmente, os desfechos primários são predominantemente subjetivos, fundamentados na frequência de crises epiléticas reportada por cuidadores. A utilização de diários de crises introduz variabilidade na qualidade dos dados, estando sujeita a vieses de percepção, memória e expectativa. Esse aspecto é particularmente relevante em contextos de epilepsia refratária pediátrica, nos quais o impacto clínico e emocional da intervenção pode influenciar o registro dos desfechos.

A distinção entre as classificações de risco de viés sério e crítico neste domínio associou-se, principalmente, ao rigor metodológico na mensuração. Estudos classificados como "sérios" tenderam a utilizar registros prospectivos e estratégias de padronização, enquanto aqueles com risco "crítico" apresentaram limitações

adicionais, como coleta retrospectiva baseada na memória ou descrição insuficiente dos métodos de aferição. Por fim, a ausência de grupos controle com procedimento simulado limita a distinção entre os efeitos fisiológicos da estimulação e as melhorias decorrentes de expectativas terapêuticas, fenômeno descrito como efeito placebo cirúrgico.

Dessa forma, a classificação uniforme no Domínio 5 reflete limitações intrínsecas à literatura disponível, devendo ser considerada na interpretação dos achados e no planejamento de pesquisas futuras.

A expectativa primária estabelecida a partir desta revisão é que haja impacto na execução de pesquisas sobre SLG e ENV. Sugere-se a adoção de padrões definidos para desfechos, quadros clínicos iniciais e estimulação elétrica pelo menos inicial. Recomenda-se também o uso de população exclusivamente com SLG na amostra, uma vez que na elaboração deste trabalho, ela foi triada para excluir a "contaminação" de dados provenientes de outras síndromes epiléticas da infância, como a Síndrome de Dravet.

Por fim, como expectativa secundária, projeta-se que estudos exclusivos sobre SLG e ENV possam definir, com maior segurança diagnóstica, o impacto da intervenção na qualidade de vida dos pacientes acometidos por essa patologia.

5 CONCLUSÃO

A presente revisão sistemática sugere que a Estimulação do Nervo Vago (ENV) pode representar uma alternativa terapêutica potencialmente útil no manejo da Síndrome de Lennox-Gastaut (SLG) refratária. Os estudos incluídos apontam benefício clínico em parcela considerável dos pacientes pediátricos avaliados, especialmente na redução de crises atônicas, tônicas e de ausência. Entretanto, a evidência disponível apresenta limitações metodológicas relevantes, com predominância de estudos retrospectivos e observacionais, além de elevado risco de viés, o que limita conclusões definitivas sobre a efetividade e a segurança da intervenção.

Além da redução na frequência das crises epilêpticas, os estudos relataram possíveis melhorias em desfechos qualitativos, particularmente no estado de alerta, na atenção e na qualidade do sono. Esses achados possuem relevância clínica, considerando que o comprometimento cognitivo associado à SLG pode ser agravado por descargas interictais persistentes, potencialmente moduladas pela neuromodulação vagal. Em relação à segurança, os efeitos adversos mais frequentemente descritos foram disfagia e alterações vocais, geralmente atribuídas aos mecanismos fisiopatológicos esperados da estimulação e, na maioria dos casos, sem necessidade de interrupção do tratamento.

A avaliação metodológica por meio do instrumento ROBINS-I identificou elevado risco de viés, sobretudo no domínio de mensuração dos desfechos, devido à ausência de cegamento e à dependência de relatos subjetivos dos cuidadores. Também foi observada heterogeneidade entre os estudos quanto aos parâmetros de estimulação, ao tempo de seguimento e às características clínicas dos pacientes. Dessa forma, reforça-se que próximos estudos devam ser coortes prospectivas e exclusivas para pacientes com SLG, com amostras representativas e protocolos padronizados de ENV, a fim de produzir evidências metodologicamente mais robustas. Enquanto não houver novos estudos neste formato, esta revisão sistemática pode guiar condutas individualizadas e assertivas no manejo da SLG.

REFERÊNCIAS

- [1] CAMFIELD, P.; CAMFIELD, C. Epileptic syndromes in childhood: clinical features, outcomes, and treatment. **Epilepsia**, v. 43 Suppl 3, p. 27–32, 2002.
- [2] ASADI-POOYA, A. Lennox-Gastaut syndrome: a comprehensive review. **NEUROLOGICAL SCIENCES**, v. 39, n. 3, p. 403–414, mar. 2018.
- [3] VIGNOLI, A. et al. Lennox–Gastaut syndrome in adulthood: Long-term clinical follow-up of 38 patients and analysis of their recorded seizures. **Epilepsy and Behavior**, v. 77, n. (Vignoli A.; Oggioni G.; Peron A., angela.peron@unimi.it; Savini M.N.; Zambrelli E.; Chiesa V.; La Briola F.; Turner K.; Canevini M.P.) Epilepsy Center, San Paolo Hospital, Milan, Italy, p. 73–78, 2017.
- [4] KOSSOFF, E. H. W.; SHIELDS, W. D. Nonpharmacologic care for patients with Lennox-Gastaut syndrome: Ketogenic diets and vagus nerve stimulation. **Epilepsia**, v. 55, n. s4, p. 29–33, 2014.
- [5] VASQUEZ, A.; FINE, A. L. Dietary therapies in Lennox-Gastaut syndrome. **Seminars in Pediatric Neurology**, v. 56, p. 101238, dez. 2025.
- [6] ARZIMANOGLU, A. et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. **The Lancet Neurology**, v. 8, n. 1, p. 82–93, jan. 2009.
- [7] SHIELDS, L. B. E.; OLUIGBO, C. O.; KARAKAS, C. Neuromodulation in Lennox-Gastaut Syndrome: Emerging therapies and future directions. **Seminars in Pediatric Neurology**, v. 56, p. 101237, dez. 2025.
- [8] GÉLISSE, P. et al. History of Lennox-Gastaut Syndrome: Sixty Years of Advancements in Therapeutic Practices. **Seizure: European Journal of Epilepsy**, v. 134, p. 165–172, jan. 2026.
- [9] SAMANTA, D.; NAIK, S. Seizure-type-specific treatment responses in Lennox-Gastaut Syndrome: A comprehensive review of pharmacological, neuromodulatory, dietary, and surgical therapies. **Epilepsy & behavior : E&B**, v. 170, p. 110472, 22 maio 2025.
- [10] SAMANTA, D. Management of Lennox-Gastaut syndrome beyond childhood: A comprehensive review. **Epilepsy and Behavior**, v. 114, n. (Samanta D., dsamanta@uams.edu) Child Neurology Section, Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, AR, United States, 2021.
- [11] SHARAWAT, I. et al. Efficacy and safety of corpus callosotomy and ketogenic diet in children with Lennox Gastaut syndrome: a systematic review and meta-analysis. **CHILDS NERVOUS SYSTEM**, v. 37, n. 8, p. 2557–2566, ago. 2021.
- [12] THIRUNAVU, V. et al. The role of surgery in the management of Lennox–Gastaut syndrome: A systematic review and meta-analysis of the clinical

- evidence. **Epilepsia**, v. 62, n. 4, p. 888–907, 2021.
- [13] SOARES, D.; DE AGUIAR, P. Callosotomy vs Vagus Nerve Stimulation in the Treatment of Lennox-Gastaut Syndrome: A Systematic Review With Meta-Analysis. **NEUROMODULATION**, v. 26, n. 3, p. 518–528, abr. 2023.
- [14] YOU, S. et al. Comparison of corpus callosotomy and vagus nerve stimulation in children with Lennox-Gastaut syndrome. **BRAIN & DEVELOPMENT**, v. 30, n. 3, p. 195–199, mar. 2008.
- [15] ARMENO, M. L.; KOSSOFF, E. H. Let food be thy medicine. The interaction between ketogenic diet therapy and anti-seizure medications: A systematic review. **Epileptic Disorders**, v. 25, n. 1, p. 18–27, fev. 2023.
- [16] LYONS, P. et al. Vagus nerve stimulation in Lennox–Gastaut syndrome: Twenty-four-month data and experience from the CORE-VNS study. **Epilepsia**, v. 66, n. 5, p. 1540–1549, 2025.
- [17] HAJNSEK, S. et al. Vagus nerve stimulation in the treatment of patients with pharmacoresistant epilepsy: our experiences. **Collegium antropologicum**, v. 35, n. 3, p. 755–760, set. 2011.
- [18] SHAHWAN, A. et al. Vagus nerve stimulation for refractory epilepsy in children: More to VNS than seizure frequency reduction. **EPILEPSIA**, v. 50, n. 5, p. 1220–1228, maio 2009.
- [19] DIBUÉ, M. et al. Vagus nerve stimulation in patients with Lennox-Gastaut syndrome: A meta-analysis. **ACTA NEUROLOGICA SCANDINAVICA**, v. 143, n. 5, p. 497–508, maio 2021.
- [20] PAGE, M. J. et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. **Systematic Reviews**, v. 10, n. 1, p. 89, 29 mar. 2021.
- [21] STERNE, J. A. et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. **BMJ (Clinical research ed.)**, v. 355, p. i4919, 12 out. 2016.
- [22] ABDELMOITY, S. et al. The efficacy and tolerability of auto-stimulation-VNS in children with Lennox-Gastaut syndrome. **SEIZURE-EUROPEAN JOURNAL OF EPILEPSY**, v. 86, p. 168–174, mar. 2021.
- [23] ALANAZI, G. M. et al. Efficacy and safety of corpus callosotomy versus vagus nerve stimulation as long-term adjunctive therapies in children with Lennox–Gastaut syndrome Experience of a tertiary care center. **Neurosciences**, v. 27, n. 2, p. 59–64, 2022.
- [24] BREMER, A. et al. Vagal nerve stimulation in children with difficult-to-treat epilepsy. **Tidsskrift for den Norske Lægeforening**, v. 126, n. 7, p. 896–898, 2006.
- [25] BUONI, S. et al. Vagus nerve stimulation for drug-resistant epilepsy in children

- and young adults. **Brain & development**, v. 26, n. 3, p. 158–163, abr. 2004.
- [26] CUKIERT, A. et al. A Prospective Long-Term Study on the Outcome After Vagus Nerve Stimulation at Maximally Tolerated Current Intensity in a Cohort of Children With Refractory Secondary Generalized Epilepsy. **NEUROMODULATION**, v. 16, n. 6, p. 551–556, nov. 2013.
- [27] CUKIERT, A. et al. Vagus Nerve Stimulation Electrode Impedance Over Time in Children With Lennox-Gastaut Syndrome. **Neuromodulation**, v. 27, n. 4, p. 789–791, 2024.
- [28] ELLIOTT, R. et al. Vagus nerve stimulation for children with treatment-resistant epilepsy: a consecutive series of 141 cases Clinical article. **JOURNAL OF NEUROSURGERY-PEDIATRICS**, v. 7, n. 5, p. 491–500, maio 2011.
- [29] FANG, T. et al. Preliminary analysis of the effect of vagus nerve stimulation in the treatment of children with intractable epilepsy. **World Journal of Clinical Cases**, v. 8, n. 23, p. 5918–5925, 2020.
- [30] FLESLE, S. et al. Vagus nerve stimulation: treatment of 158 pediatric patients with a long-term follow-up. **REVISTA DE NEUROLOGIA**, v. 64, n. 11, p. 496–501, 1 jun. 2017.
- [31] FROST, M. et al. Vagus nerve stimulation in children with refractory seizures associated with Lennox-Gastaut syndrome. **EPILEPSIA**, v. 42, n. 9, p. 1148–1152, set. 2001.
- [32] HALLBÖÖK, T. et al. Vagus nerve stimulation in 15 children with therapy resistant epilepsy; its impact on cognition, quality of life, behaviour and mood. **SEIZURE-EUROPEAN JOURNAL OF EPILEPSY**, v. 14, n. 7, p. 504–513, out. 2005.
- [33] HENTATI, E. et al. Surgical palliative care in Lennox-Gastaut syndrome. **Journal of the Neurological Sciences**, v. 333, n. (Hentati E.; Ben Ali N.; Kchaou M.; Belal S.) Service de Neurologie, Hopital Charles Nicolle, Tunis, Tunisia, p. e50, 2013.
- [34] HOSAIN, S. et al. Vagus nerve stimulation treatment for Lennox-Gastaut syndrome. **Journal of child neurology**, v. 15, n. 8, p. 509–512, ago. 2000.
- [35] KATAGIRI, M. et al. Combined surgical intervention with vagus nerve stimulation following corpus callosotomy in patients with Lennox-Gastaut syndrome. **Acta Neurochirurgica**, v. 158, n. 5, p. 1005–1012, 2016.
- [36] KRUSE, B. et al. Vagus nerve stimulation in epileptic encephalopathies. **Zeitschrift für Epileptologie**, v. 23, n. 3, p. 189–193, 2010.
- [37] LAGAE, L.; VERSTREPEN, A.; JANSEN, K. Vagus nerve stimulation in children with refractory epilepsy: Age at implantation as a predictor of better efficacy. **Paediatrica Croatica**, v. 56, n. 2, p. 105–109, 2012.
- [38] LUNDGREN, J. et al. Vagus nerve stimulation in 16 children with refractory

- epilepsy. **Epilepsia**, v. 39, n. 8, p. 809–813, 1998.
- [39] MAJOIE, H. J. M. et al. Vagus nerve stimulation in patients with catastrophic childhood epilepsy, a 2-year follow-up study. **Seizure**, v. 14, n. 1, p. 10–18, 2005.
- [40] MIKATI, M. A. et al. Quality of life after vagal nerve stimulator insertion. **Epileptic Disorders**, v. 11, n. 1, p. 67–74, 2009.
- [41] OROSZ, I. et al. Vagus nerve stimulation for drug-resistant epilepsy: A European long-term study up to 24 months in 347 children. **Epilepsia**, v. 55, n. 10, p. 1576–1584, 2014.
- [42] PARKER, A. P. J. et al. Vagal nerve stimulation in epileptic encephalopathies. **Pediatrics**, v. 103, n. 4 I, p. 778–782, 1999.
- [43] PRETO MIMURA, P. M. et al. Follow-up of neuropediatric patients treated with vagus nerve stimulation. **Journal of the Neurological Sciences**, v. 381, n. (Preto Mimura P.M.) Hospital Francisco Ribeiro Arantes, Medical, Itu, Brazil, p. 683, 2017.
- [44] ROSSIGNOL, E. et al. Vagus nerve stimulation in pediatric epileptic syndromes. **Seizure**, v. 18, n. 1, p. 34–37, 2009.
- [45] RYCHLICKI, F. et al. Vagus nerve stimulation: clinical experience in drug-resistant pediatric epileptic patients. **Seizure**, v. 15, n. 7, p. 483–490, out. 2006.
- [46] TEKIN, H. et al. The Effect of Vagal Nerve Stimulation on the Quality of Life in Pediatric Cases. **JOURNAL OF PEDIATRIC RESEARCH**, v. 4, n. 3, p. 137–142, set. 2017.
- [47] TORMASIOVA, M.; KOLLOVA, A.; BRATSKY, L. Immediate postimplantation effect of baseline stimulation parameters of vagus nerve stimulation in patients with refractory epilepsy. **Stereotactic and Functional Neurosurgery**, v. 92, n. (Tormasiova M.) Dept. of Neurology, University Hospital Kosice, Kosice, Slovakia, p. s216, 2014.
- [48] ZAMPONI, N. et al. Effectiveness of vagal nerve stimulation (VNS) in patients with drop-attacks and different epileptic syndromes. **Seizure**, v. 20, n. 6, p. 468–474, 2011.
- [49] MORRIS, G. L. et al. Evidence-based guideline update: Vagus nerve stimulation for the treatment of epilepsy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. **Neurology**, v. 81, n. 16, p. 1453–1459, 15 out. 2013.
- [50] RYVLIN, P. et al. Neuromodulation in epilepsy: state-of-the-art approved therapies. **The Lancet Neurology**, v. 20, n. 12, p. 1038–1047, dez. 2021.
- [51] GUERRINI, R. Epilepsy in children. **The Lancet**, v. 367, n. 9509, p. 499–524, fev. 2006.

- [52] WARREN, A. E. L. et al. Abnormal cognitive network interactions in Lennox-Gastaut syndrome: A potential mechanism of epileptic encephalopathy. **Epilepsia**, v. 57, n. 5, p. 812–822, maio 2016.
- [53] BRIGO, F. et al. Anti-seizure medications for Lennox-Gastaut syndrome. **Cochrane Database of Systematic Reviews**, v. 2022, n. 9, 7 abr. 2021.
- [54] ELGER, C. E.; HELMSTAEDTER, C.; KURTHEN, M. Chronic epilepsy and cognition. **The Lancet Neurology**, v. 3, n. 11, p. 663–672, nov. 2004.
- [55] PINO, A. F.; NAIK, S.; ERDEMIR, G. Lennox-Gastaut syndrome: Comorbidities and clinical implications. **Seminars in Pediatric Neurology**, v. 56, p. 101239, dez. 2025.
- [56] GIORDANO, F. et al. Vagus nerve stimulation: Surgical technique of implantation and revision and related morbidity. **Epilepsia**, v. 58, n. (Giordano F., flavio.giordano@meyer.it; Genitori L.) Department of Neurosurgery, Anna Meyer Hospital, University of Firenze, Firenze, Italy, p. 85–90, 2017.
- [57] LYUBASHINA, O. A.; SOKOLOV, A. Y.; PANTELEEV, S. S. Vagal afferent modulation of spinal trigeminal neuronal responses to dural electrical stimulation in rats. **Neuroscience**, v. 222, p. 29–37, out. 2012.

ANEXO A - ORIENTAÇÕES PARA AUTORES DA REVISTA EPILEPSY & BEHAVIOR



Epilepsy & Behavior

Supports open access

Guide for authors

About the journal

- Aims and scope • Article types
- Peer review Open access

Ethics and policies

- Ethics in publishing Submission declaration Authorship
- Changes to authorship Declaration of competing interests Funding sources
- Declaration of generative AI use Preprints
- Use of inclusive language
- Reporting sex- and gender-based analyses Jurisdictional claims
- Studies in humans Studies in animals Delayed publication

Writing and formatting

- File format Title page Abstract Keywords Highlights
- Graphical abstract
- Units, classifications codes and nomenclature Math formulae
- Tables
- Figures, images and artwork
- Generative AI and Figures, images and artwork Supplementary material
- Video
- Research data Data statement
- Data linking
- Co-submission of related data, methods or protocols Article structure
- References

Submitting your manuscript

- Submission checklist Submit online

After receiving a final decision

- Article Transfer Service Publishing agreement License options
- Open access
- Permission for copyrighted works Proof correction
- Share Link Responsible sharing

Resources for authors

- Elsevier Researcher Academy Language and editing services

Getting help and support

- Author support

Continua

About the journal

Aims and scope

Epilepsy & Behavior is the fastest-growing international journal uniquely devoted to the rapid dissemination of the most current information available on the behavioral aspects of seizures and epilepsy.

Epilepsy & Behavior presents original peer-reviewed articles based on laboratory and clinical research. Topics are drawn from a variety of fields, including clinical neurology, neurosurgery, neuropsychiatry, neuropsychology, neurophysiology, neuropharmacology, and neuroimaging.

Epilepsy & Behavior publishes papers on the study of:

- Localization of ictal and postictal behaviors
- Neuroendocrine aspects of epilepsy
- Psychiatric and psychosocial aspects of epilepsy
- Behavioral aspects of epilepsy surgery
- Cognitive and affective effects of seizure treatment
- Functional imaging
- Animal models

Letters to the Editor will only be considered if they comment on articles that were previously published in *Epilepsy & Behavior*. The journal does not publish Case Reports. Authors who submit these to *Epilepsy & Behavior* will be offered a transfer or asked to resubmit their Case Reports to the journal's companion title, *Epilepsy & Behavior Reports*.

Cited in MEDLINE/PubMed and Index Medicus, Current Contents/Clinical Medicine, Science Citation Index-Expanded, Neuroscience Citation Index, PsychINFO, and EMBASE.

Article types

Epilepsy & Behavior publishes the following types of articles:

- Original research articles (both clinical and laboratory research)
- Reviews
- Editorials
- Brief communications
- Letters
- Book reviews
- Calendar of events

Reviews: Please note that only unsolicited systematic reviews will be considered for publication. Authors are required to register the protocol for the systematic review before data extraction on an accessible, searchable site such as PROSPERO and include registration number.

Editorials: Please note that Editorials are only commissioned and they comment on articles published in *Epilepsy & Behavior*.

Letters: Please note that only letters to the Editor commenting on papers published in *Epilepsy & Behavior* will be considered for publication.

Continua

Peer review

This journal follows a single anonymized review process. Your submission will initially be assessed by our editors to determine suitability for publication in this journal. If your submission is deemed suitable, it will typically be sent to a minimum of one reviewer for an independent expert assessment of the scientific quality. The decision as to whether your article is accepted or rejected will be taken by our editors. Read more about peer review.

Our editors are not involved in making decisions about papers which:

- * they have written themselves.
- * have been written by family members or colleagues.
- * relate to products or services in which they have an interest.

Any such submissions will be subject to the journal's usual procedures and peer review will be handled independently of the editor involved and their research group. Read more about editor duties.

Authors may submit a formal appeal request to the editorial decision, provided it meets all the requirements and follows the procedure outlined in Elsevier's Appeal Policy. Only one appeal per submission will be considered and the appeal decision will be final.

Special issues and article collections

The peer review process for special issues and article collections follows the same process as outlined above for regular submissions, except, a guest editor may send the submissions out to the reviewers and may recommend a decision to the journal editor. The journal editor oversees the peer review process of all special issues and article collections to ensure the high standards of publishing ethics and responsiveness are respected and is responsible for the final decision regarding acceptance or rejection of articles.

Open access

We refer you to our open access information page to learn about open access options for this journal.

Ethics and policies

Ethics in publishing

Authors must follow ethical guidelines stated in Elsevier's Publishing Ethics Policy.

Submission declaration

When authors submit an article to an Elsevier journal it is implied that:

- * the work described has not been published previously except in the form of a preprint, an abstract, a published lecture, academic thesis or registered report. See our policy on multiple, redundant or concurrent publication.
- * the article is not under consideration for publication elsewhere.
- * the article's publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out.
- * if accepted, the article will not be published elsewhere in the same form, in English or in any other language, including electronically, without the written consent of the copyright-holder.

To verify compliance with our journal publishing policies, we may check your manuscript with our screening tools.

Authorship

Continua

All authors should have made substantial contributions to all of the following:

1. The conception and design of the study, or acquisition of data, or analysis and interpretation of data
2. Drafting the article or revising it critically for important intellectual content.
3. Final approval of the version to be submitted.

All authors are accountable for all aspects of the work, to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Authors should appoint a single corresponding author to communicate with the journal during the editorial process. This individual submits the manuscript and all required documentation to the journal, and serves as the primary contact between the journal and the co-authors. Only the corresponding author's affiliation will be used to determine eligibility for a publishing agreement, and possible discounts related to it. Affiliations of other co-authors are not relevant for eligibility.

Changes to authorship

The editors of this journal generally will not consider changes to authorship once a manuscript has been submitted. It is important that authors carefully consider the authorship list and order of authors and provide a definitive author list at submission.

The policy of this journal around authorship changes:

- * All authors must be listed in the manuscript and their details entered into the submission system. Changes can only be made prior to acceptance, and only if approved by the journal editor. This includes additions, deletion, or rearrangement of author names.
- * Requests to change authorship must be made by the corresponding author using the Authorship Change Request form. The corresponding author must provide the reason for the request to the journal editor with written confirmation from all authors, including any authors being added or removed, that they agree with the changes. Requests which do not comply with the instructions outlined in the form will not be considered.
- * This journal does not allow authorship changes after acceptance. This includes additions, deletions, or the rearrangement of author names, including changes to the corresponding author.
- * The review process may be paused while a change in authorship request is being considered.
- * Change requests made by the authors without the Authorship Change Request form or editor approval may result in the rejection of the manuscript, or retraction if the article has already been published.

Declaration of competing interests

All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence or bias their work. Examples of potential competing interests include:

- * Employment
- * Consultancies
- * Stock ownership
- * Honoraria

Continua

- * Paid expert testimony
 - * Patent applications or registrations
 - * Grants or any other funding
 - * Affiliation with the journal as an Editor or Advisory Board Member
- The declarations tool should always be completed.

Authors with a journal affiliation to declare should enter the following text under “Other Activities” within the declarations tool and should inform the journal and publisher prior to completing the submission process:

Given their role as [insert journal role title], [insert your name] had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to another journal editor.

Editorial disclosure statements will be included as a footnote and/or in the declaration of competing interest section of the article. Authors with no competing interests to declare should select the option "I have nothing to declare".

The resulting Word document containing your declaration should be uploaded at the "attach/upload files" step in the submission process. It is important that the Word document is saved in the .doc/.docx file format. Author signatures are not required.

Funding sources

Authors must disclose any funding sources who provided financial support for the conduct of the research and/or preparation of the article. The role of sponsors, if any, should be declared in relation to the study design, collection, analysis and interpretation of data, writing of the report and decision to submit the article for publication. If funding sources had no such involvement this should be stated in your submission.

List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants, scholarships and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.

If no funding has been provided for the research, it is recommended to include the following sentence:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of generative AI use

Authors must declare the use of generative AI in the manuscript preparation process upon submission of the paper.

Elsevier recognizes the potential of generative AI and AI-assisted technologies (“AI Tools”), when used responsibly, to help researchers work efficiently, gain critical insights fast and achieve better outcomes. Increasingly, these tools, including AI agents and deep research tools, are helping researchers to synthesize complex literature, provide an overview of a field or research question, identify research gaps, generate ideas, and provide tailored support for tasks such as content organization and improving language and readability.

Authors preparing a manuscript for this journal can use AI Tools to support them. However, these tools must never be used as a substitute for human critical thinking, expertise and evaluation. AI technology should always be applied with human oversight and control.

Ultimately, authors are responsible and accountable for the contents of their work. This includes accountability for:

- * Carefully reviewing and verifying the accuracy, comprehensiveness, and impartiality of all AI-generated output (including checking the sources, as AI-generated references can be incorrect or fabricated).
- * Editing and adapting all material thoroughly to ensure the manuscript represents the author's authentic and original contribution and reflects their own analysis, interpretation, insights and ideas.
- * Ensuring the use of any tools or sources, AI-based or otherwise, is made clear and transparent to readers. If AI Tools have been used, we require a disclosure statement upon submission; please see example below.
- * Ensuring the manuscript is developed in a way that safeguards data privacy, intellectual property and other rights, by checking the terms and conditions of any AI tool that is used.

Finally, authors must not list or cite AI Tools as an author or co-author on the manuscript since authorship implies responsibilities and tasks that can only be attributed to, and performed by, humans.

The use of AI Tools in the manuscript preparation process must be declared by adding a statement at the end of the manuscript when the paper is first submitted. The statement will appear in the published work and should be placed in a new section before the references list.

An example:

- * Title of new section: *Declaration of generative AI and AI-assisted technologies in the manuscript preparation process.*
- * Statement: *During the preparation of this work the author(s) used [NAME OF TOOL / SERVICE] in order to [REASON]. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the published article.*

The declaration does not apply to the use of basic tools, such as tools used to check grammar, spelling and references. If you have nothing to disclose, you do not need to add a statement.

Please read Elsevier's author policy on the use of generative AI and AI-assisted technologies, which can be found in the generative AI policies for journals.

Please note: to protect authors' rights and the confidentiality of their research, this journal does not currently allow the use of generative AI or AI-assisted technologies such as ChatGPT or similar services by reviewers or editors in the peer review and manuscript evaluation process, as is stated in Elsevier's generative AI policies for journals. Elsevier is actively evaluating compliant AI Tools and may revise this policy in the future.

Preprints

Preprint sharing

Authors may share preprints in line with Elsevier's article sharing policy. Sharing preprints, such as on a preprint server, will not count as prior publication.

We advise you to read our policy on multiple, redundant or concurrent publication.

Continua

Use of inclusive language

Inclusive language acknowledges diversity, conveys respect to all people, is sensitive to differences, and promotes equal opportunities. Authors should ensure their work uses inclusive language throughout and contains nothing which might imply one individual is superior to another on the grounds of:

- * age
- * gender
- * race
- * ethnicity
- * culture
- * sexual orientation
- * disability or health condition

We recommend avoiding the use of descriptors about personal attributes unless they are relevant and valid. Write for gender neutrality with the use of plural nouns ("clinicians, patients/clients") as default. Wherever possible, avoid using "he, she," or "he/she."

No assumptions should be made about the beliefs of readers and writing should be free from bias, stereotypes, slang, reference to dominant culture and/or cultural assumptions.

These guidelines are meant as a point of reference to help you identify appropriate language but are by no means exhaustive or definitive.

Reporting sex- and gender-based analyses

There is no single, universally agreed-upon set of guidelines for defining sex and gender. We offer the following guidance:

- * Sex and gender-based analyses (SGBA) should be integrated into research design when research involves or pertains to humans, animals or eukaryotic cells. This should be done in accordance with any requirements set by funders or sponsors and best practices within a field.
- * Sex and/or gender dimensions of the research should be addressed within the article or declared as a limitation to the generalizability of the research.
- Definitions of sex and/or gender applied should be explicitly stated to enhance the precision, rigor and reproducibility of the research and to avoid ambiguity or conflation of terms and the constructs to which they refer.

We advise you to read the Sex and Gender Equity in Research (SAGER) guidelines and the SAGER checklist (PDF) on the EASE website, which offer systematic approaches to the use of sex and gender information in study design, data analysis, outcome reporting and research interpretation.

For further information we suggest reading the rationale behind and recommended use of the SAGER guidelines.

Definitions of sex and/or gender

We ask authors to define how sex and gender have been used in their research and publication. Some guidance:

Continua

- * Sex generally refers to a set of biological attributes that are associated with physical and physiological features such as chromosomal genotype, hormonal levels, internal and external anatomy. A binary sex categorization (male/female) is usually designated at birth ("sex assigned at birth") and is in most cases based solely on the visible external anatomy of a newborn. In reality, sex categorizations include people who are intersex/have differences of sex development (DSD).
- * Gender generally refers to socially constructed roles, behaviors and identities of women, men and gender-diverse people that occur in a historical and cultural context and may vary across societies and over time. Gender influences how people view themselves and each other, how they behave and interact and how power is distributed in society.

Depending on the focus of a paper, sex and/or gender may or may not be relevant to the content of the paper. We recognize that beliefs, attitudes, and laws relating to sex and gender may vary. These articles do not attempt to dictate author beliefs but rather require that, where relevant to an author's research or paper, the author must provide clear explanations of how the paper and research define and use sex and gender.

Jurisdictional claims

Elsevier respects the decisions taken by its authors as to how they choose to designate territories and identify their affiliations in their published content. Elsevier's policy is to take a neutral position with respect to territorial disputes or jurisdictional claims, including, but not limited to, maps and institutional affiliations. For journals that Elsevier publishes on behalf of a third party owner, the owner may set its own policy on these issues.

Maps: Readers should be able to locate any study areas shown within maps using common mapping platforms. Maps should only show the area actually studied and authors should not include a location map which displays a larger area than the bounding box of the study area. Authors should add a note clearly stating that "*map lines delineate study areas and do not necessarily depict accepted national boundaries*". During the review process, Elsevier's editors may request authors to change maps if these guidelines are not followed.

- Institutional affiliations: Authors should use either the full, standard title of their institution or the standard abbreviation of the institutional name so that the institutional name can be independently verified for research integrity purposes.

Studies in humans

Authors must follow ethical guidelines for research involving humans, their data, and/or their biological materials (e.g. organs, tissues). Authors should ensure that they adhere to the following:

- * All studies must be performed in compliance with relevant laws, regulations, and institutional guidelines and that the appropriate institutional committee(s) has/have approved them. For instance, medical research involving humans should be carried out in accordance with the World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human participants and should follow the International Committee of Medical Journal Editors (ICMJE) recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals and aim to be representative of human populations in terms of sex, age and ethnicity. Sex and gender terms should be used correctly, as outlined in the "Reporting Sex- and Gender-based analyses" section of this journal's Guide for Authors.
- * Informed consent must be obtained for research with human participants, including their data or biological materials. Consent must be given without coercion, and the privacy rights of human participants must always be observed. If your study contains human participants, please read Elsevier's full human research policy for further information.

Continua

- Authors should be aware that written (or electronic) consent is required for certain studies under national laws. In studies where only verbal informed consent was obtained, authors should include justification for the absence of written consent, the name of the approving ethics committee, and a statement on how verbal consent was recorded.
- Consent for publication should also be obtained.
- * Authors must obtain and retain explicit written consent for any identifiable participant materials (e.g. case details, videos, recordings, images, photographs, and illustrations). All participant information must be de-identified: do not include names or personal identifiers (e.g., initials, ID numbers, DOB)
- * Images should be used only when scientifically necessary and with explicit consent, and nonessential identifying details must be removed. If identifiers are altered to ensure anonymity, authors must confirm that scientific meaning is not affected. Fully anonymized images (e.g., x-rays, scans) that contain no identifying marks and are not accompanied by identifying text do not require formal consent, though informing the patient is good practice. Case reports always require consent. Simply obscuring identity (e.g., eye bars or blurring) is not sufficient without consent.
- * Written consents must be retained by the authors. They should not be provided to this journal unless this is specifically requested in exceptional circumstances, for example, when a legal issue arises. Only then should you provide copies of the consents, or evidence that all relevant consents were obtained.
- * Appropriate consents and safeguards should be in place for research with vulnerable populations, as described in Elsevier's human research policy. In many countries, additional ethical approval may be needed for research with those who lack the capacity to consent (e.g. children or those with mental health or neurological conditions including dementia).
- * For the full policy, see "Consent requirements for case reports, personal information, and images."

All studies involving human participants require a statement that details any ethical approval(s), guidelines followed, confirmation of informed consent, and any other necessary information in line with Elsevier's human research policy. The statement should contain the date and reference number of any ethical approval(s) obtained

If ethical approval is not required by national laws or where a study has been granted an exemption from an ethics committee, the statement must explain why the study is exempt and confirm that the appropriate protocols for protecting the rights and privacy of all participants were utilized during the execution of the research (e.g. no coercion to participate, full disclosure of study requirements and risks, consent of participants (or their Legal Representatives), no release of participant data without their knowledge, etc.).

Human biological material

For all studies that use human organs or tissues, sufficient evidence must be provided that these were procured in line with WHO Guiding Principles on Human Cell, Tissue and Organ Transplantation. The source of the organs or tissues used in clinical research must be transparent and traceable and must not be sourced from executed prisoners or prisoners of conscience, consistent with recommendations by Global Rights Compliance on Mitigating Human Rights Risks in Transplantation Medicine.

For clinical studies, a statement of informed consent having been obtained from a patient or their legal representative, paired with ethical approval for the study from a suitable institution, as required by the policies of the journal, may be considered sufficient evidence, but the journal reserves the right to request additional evidence in cases where it feels this is not sufficient.

Continua

If the manuscript describes organ transplantation authors must additionally declare within the manuscript that:

- * Autonomous consent, free from coercion, was obtained from the donor(s) or their next of kin.
- * Organs and/or tissues were not sourced from executed prisoners or prisoners of conscience.

Studies in animals

All animal experiments should comply with the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines (or national equivalent) and should be carried out in accordance with relevant laws and associated guidelines for animal welfare. This may include the U.K. Animals (Scientific Procedures) Act 1986; the EU Directive 2010/63/EU on the protection of animals used for scientific purposes; the National Research Council Guide for the Care and Use of Laboratory Animals; or those of an equivalent internationally recognized body.

Authors must ensure that the manuscript contains a statement that confirms which guidelines have been followed. This statement should include the ethics committee approval number, when available. If a study was granted exemption or did not require ethics approval, a statement detailing this should be included in the manuscript.

The sex of animals, and where appropriate, the influence (or association) of sex on the results of the study should be indicated.

Where applicable, researchers are encouraged to document informed consent from the client or owner in studies involving client-owned animals and adhere to best practices of veterinary care. For research on threatened and/or endangered species, authors are advised to consult international best practice guidelines such as the International Union for Conservation of Nature (IUCN) Policy Statement on Research Involving Species at Risk of Extinction and IUCN red list guidelines.

Delayed publication

If you need to delay the publication of your article for any reason, please contact the editorial office of the journal or our Journal Article Publishing Support Center at the earliest possible opportunity. While we will try to ensure that your article is not published before a certain date if you make your request on a timely basis, we cannot guarantee this. Please also note that once the agreed period of delay has expired the article may be published at any time thereafter.

Writing and formatting

File format

We ask you to provide editable source files for your entire submission (including figures, tables and text graphics). Some guidelines:

- * Save files in an editable format, using the extension .doc/.docx for Word files and .tex for LaTeX files. A PDF is not an acceptable source file.
- * Format Word files in a single-column layout. Double-column formatting is only permitted for LaTeX submissions.
- * Remove any strikethrough and underlined text from your manuscript, unless it has scientific significance related to your article.
- * Use spell-check and grammar-check functions to avoid errors.

We advise you to read our Step-by-step guide to publishing with Elsevier.

Title page

You are required to include the following details in the title page information:

- **Article title.** Article titles should be concise and informative. Please avoid abbreviations and formulae, where possible, unless they are established and widely understood, e.g. DNA.
- **Author names.** Provide the given name(s) and family name(s) of each author. The order of authors should match the order in the submission system. Carefully check that all names are accurately spelled. If needed, you can add your name between parentheses in your own script after the English transliteration.
- **Affiliations.** Add affiliation addresses, referring to where the work was carried out, below the author names. Indicate affiliations using a lower-case superscript letter immediately after the author's name and in front of the corresponding address. Ensure that you provide the full postal address of each affiliation, including the country name and, if available, the email address of each author.
- **Corresponding author.** Clearly indicate who will handle correspondence for your article at all stages of the refereeing and publication process and also post-publication. This responsibility includes answering any future queries about your results, data, methodology and materials. It is important that the email address and contact details of your corresponding author are kept up to date during the submission and publication process. Present/permanent address. If an author has moved since the work described in your article was carried out, or the author was visiting during that time, a "present address" (or "permanent address") can be indicated by a footnote to the author's name. The address where the author carried out the work must be retained as their main affiliation address. Use superscript Arabic numerals for such footnotes.

Abstract

You are required to provide a concise and factual abstract which does not exceed 250 words. The abstract should briefly state the purpose of your research, principal results and major conclusions. Some guidelines:

- Abstracts must be able to stand alone as abstracts are often presented separately from the article.
- Avoid references. If any are essential to include, ensure that you cite the author(s) and year(s).
- Avoid non-standard or uncommon abbreviations. If any are essential to include, ensure they are defined within your abstract at first mention.

Keywords

You are required to provide 1 to 7 keywords for indexing purposes. Keywords should be written in English. Please try to avoid keywords consisting of multiple words (using "and" or "of").

We recommend that you only use abbreviations in keywords if they are firmly established in the field.

Highlights

You are encouraged to provide article highlights at submission.

Highlights are a short collection of bullet points that should capture the novel results of your research as well as any new methods used during your study. Highlights will help increase the discoverability of your article via search engines. Some guidelines:

- Submit highlights as a separate editable file in the online submission system with the word "highlights" included in the file name.
- Highlights should consist of 3 to 5 bullet points, each a maximum of 85 characters, including spaces.

We encourage you to view example article highlights and read about the benefits of their inclusion.

Graphical abstract

You are required to provide a graphical abstract at submission.

The graphical abstract summarizes the contents of your article in a concise, pictorial, professional form, highlighting important aspects of the research. It is designed to appeal to an interdisciplinary audience, and draw more attention to your online article. Some guidelines:

- Ensure you have obtained the necessary permission to include any third party owned material in a graphical abstract.
- Use of generative AI or AI-assisted tools in the production of graphical abstracts must align with Elsevier's [GenAI Policies for Journals](#).
- Submit your graphical abstract as a separate file in the online submission system.
- Ensure the image is 531 x 1328 pixels (h x w) or proportionally more, and is readable at a size of 5 x 13 cm.
- Preferred file types for graphical abstracts are TIFF, EPS, PDF or MS Office files.

More information, examples and a template can be found in the graphical abstract guidelines.

Units, classifications codes and nomenclature

Units

This journal requires you to use the international system of units (SI) which follows internationally accepted rules and conventions. If other units are mentioned within your article, you should provide the equivalent unit in SI.

Math formulae

- Submit math equations as editable text, not as images.
- Present simple formulae in line with normal text, where possible.
- Use the solidus (/) instead of a horizontal line for small fractional terms such as X/Y.
- Present variables in italics.
- Denote powers of e by exp.
- Display equations separately from your text, numbering them consecutively in the order they are referred to within your text.

Tables

Tables must be submitted as editable text, not as images. Some guidelines:

- Place tables next to the relevant text or on a separate page(s) at the end of your article.
- Cite all tables in the manuscript text.
- Number tables consecutively according to their appearance in the text.
- Please provide captions along with the tables.
- Place any table notes below the table body.
- Avoid vertical rules and shading within table cells.

Continua

We recommend that you use tables sparingly, ensuring that any data presented in tables is not duplicating results described elsewhere in the article.

Figures, images and artwork

Figures, images, artwork, diagrams and other graphical media must be supplied as separate files along with the manuscript. We recommend that you read our detailed artwork and media instructions. Some excerpts:

When submitting artwork:

- * Cite all images in the manuscript text.
- * Number images according to the sequence they appear within your article.
- * Submit each image as a separate file using a logical naming convention for your files (for example, Figure_1, Figure_2 etc).
- * Text graphics may be embedded in the text at the appropriate position. If you are working with LaTeX, text graphics may also be embedded in the file.

Figure captions

All images must have a caption. A caption should consist of a brief title (not displayed on the figure itself) and a description of the image. We advise you to keep the amount of text in any image to a minimum, though any symbols and abbreviations used should be explained.

Read how to add captions to your submission [here](#).

Artwork formats

When your artwork is finalized, "save as" or convert your electronic artwork to the formats listed below taking into account the given resolution requirements for line drawings, halftones, and line/halftone combinations:

- * Vector drawings: Save as EPS or PDF files embedding the font or saving the text as "graphics."
- * Color or grayscale photographs (halftones): Save as TIFF, JPG or PNG files using a minimum of 300 dpi (for single column width: min. 1063 pixels, full page width: 2244 pixels).
- * Bitmapped line drawings: Save as TIFF, JPG or PNG files, using a minimum of 1000 dpi (for single column width: min. 3543 pixels, full page width: 7480 pixels).
- * Combinations bitmapped line/halftones (color or grayscale): Save as TIFF, JPG or PNG files using a minimum of 500 dpi (for single column: min. 1772 pixels, full page width: 3740 pixels).

Please do not submit:

- * Files that are too low in resolution.
- * Disproportionally large images compared to font size, as text may become unreadable.

Color artwork

If you submit usable color figures with your accepted article, we will ensure that they appear in color online.

Please ensure that color images are accessible to all, including those with impaired color vision. [Learn more about color and web accessibility.](#)

Continua

Generative AI and Figures, images and artwork

Please read our policy on the use of generative AI and AI-assisted tools in figures, images and artwork, which can be found in Elsevier's [GenAI Policies for Journals](#). This policy states:

- * We do not permit the use of Generative AI or AI-assisted tools to create or alter images in submitted manuscripts.
- * The only exception is if the use of AI or AI-assisted tools is part of the research design or methods (for example, in the field of biomedical imaging). If this is the case, such use must be described in a reproducible manner in the methods section, including the name of the model or tool, version and extension numbers, and manufacturer.
- * The use of generative AI or AI-assisted tools in the production of artwork such as for graphical abstracts is not permitted. The use of generative AI in the production of cover art may in some cases be allowed, if the author obtains prior permission from the journal editor and publisher, can demonstrate that all necessary rights have been cleared for the use of the relevant material, and ensures that there is correct content attribution.

Supplementary material

We encourage the use of supplementary materials such as applications, images and sound clips to enhance research. Some guidelines:

- * Supplementary material should be accurate and relevant to the research.
- * Cite all supplementary files in the manuscript text.
- * Submit all supplementary materials at the same time as your manuscript.
- * Include a concise, descriptive caption for each supplementary file, describing its content.
- * After submission supplementary files can only be added or replaced in the revision stage of the editorial process.
- * Be aware that all supplementary materials provided will appear online in the exact same way as received. These files will not be checked, formatted or typeset by the production team.

Video

This journal accepts video material and animation sequences to support and enhance your scientific research. We encourage you to include links to video or animation files within articles. Some guidelines:

- * When including video or animation file links within your article, refer to the video or animation content by adding a note in your text where the file should be placed.
- * Clearly label files ensuring the given file name is directly related to the file content.
- * Provide files in one of our recommended file formats. Files should be within our preferred maximum file size of 150 MB per file, 1 GB in total.
- * Provide "stills" for each of your files. These will be used as standard icons to personalize the link to your video data. You can choose any frame from your video or animation or make a separate image.
- * Provide descriptive text in your manuscript to refer to the video content. This text helps ensure accessibility for visually impaired readers who rely on descriptive information. For journals publishing in print this is also essential, as video and animation files cannot be embedded in the print version.

We publish all video and animation files supplied in the electronic version of your article.

Continua

For more detailed instructions, we recommend that you read our guidelines on submitting video content to be included in the body of an article.

Research data

We are committed to supporting the storage of, access to and discovery of research data, and our research data policy sets out the principles guiding how we work with the research community to support a more efficient and transparent research process.

Research data refers to the results of observations or experimentation that validate research findings, which may also include software, code, models, algorithms, protocols, methods and other useful materials related to the project.

Please read our guidelines on sharing research data for more information on depositing, sharing and using research data and other relevant research materials.

Research data deposit, citation and linking

For this journal, **Option B** instructions from our research data guidelines apply. This means that you are **encouraged** to:

- * Deposit your research data in a relevant data repository.
- * Cite and link to this dataset in your article.
- * If this is not possible, make a statement explaining why research data cannot be shared.

Data statement

To foster transparency, you are encouraged to state the availability of any data at submission.

Ensuring data is available may be a requirement of your funding body or institution. If your data is unavailable to access or unsuitable to post, you can state the reason why (e.g., your research data includes sensitive or confidential information such as patient data) during the submission process. This statement will appear with your published article on ScienceDirect.

Read more about the importance and benefits of providing a data statement.

Data linking

Linking to the data underlying your work increases your exposure and may lead to new collaborations. It also provides readers with a better understanding of the described research.

If your research data has been made available in a data repository there are a number of ways your article can be linked directly to the dataset:

- * Provide a link to your dataset when prompted during the online submission process.
- * For some data repositories, a repository banner will automatically appear next to your published article on ScienceDirect.
- * You can also link relevant data or entities within the text of your article through the use of identifiers. Use the following format: Database: 12345 (e.g. TAIR: AT1G01020; CCDC: 734053; PDB: 1XFN).

Learn more about linking research data and research articles in ScienceDirect.

Co-submission of related data, methods or protocols

You are encouraged to publish a description of your research data, methods, or protocols related to your regular article as a co-submission article in

[Data in Brief](#) or *[MethodsX](#)*.

This co-submission can be submitted at the same time as your regular manuscript submission to this journal. If both your regular and co-submitted manuscripts are accepted for publication, they will be linked together on ScienceDirect, thereby promoting research reproducibility, interoperability, and open science.

- * Prepare a separate manuscript describing your research data, methods, or protocols using the **mandatory templates** from *[Data in Brief](#)* or in *[MethodsX](#)*.
- * Submit this co-submission alongside your regular manuscript as a separate submission item; on the 'Attach files' page in Editorial Manager, after which it will be automatically forwarded to the *[Data in Brief](#)* or *[MethodsX](#)* and assigned an editor.
- * For associated Article Processing Charge (APC) details, please visit:
 - [MethodsX](#)
 - [Data in Brief](#)

Please note: Due to the automated process of submitting to *[Data in Brief](#)* or *[MethodsX](#)*, only after acceptance will you be presented with a personalized OA Article Publishing Charge based on your individual context (your country, institutional affiliation, and any society membership for example).

Please visit [co-submission Researcher Support page](#) for more information on how to submit a co-submission.

Article structure

Article sections

- * Divide your article into clearly defined and numbered sections. Number subsections 1.1 (then 1.1.1, 1.1.2, ...), then 1.2, etc.
- * Use the numbering format when cross-referencing within your article. Do not just refer to "the text."
- * You may give subsections a brief heading. Headings should appear on a separate line.
 - Do not include the article abstract within section numbering.

Footnotes

We advise you to use footnotes sparingly. If you include footnotes in your article, ensure that they are numbered consecutively.

You may use system features that automatically build footnotes into text. Alternatively, you can indicate the position of footnotes within the text and present them in a separate section at the end of your article.

Acknowledgements

Include any individuals who provided you with help during your research, such as help with language, writing or proof reading, in the acknowledgements section.

Acknowledgements should be placed in a separate section which appears directly before the reference list. Do not include acknowledgements on your title page, as a footnote to your title, or anywhere else in your article other than in the separate acknowledgements section.

Author contributions: CRediT

Corresponding authors are required to acknowledge co-author contributions using CRediT (Contributor Roles Taxonomy) roles:

- * Conceptualization
- * Data curation
- * Formal analysis
- * Funding acquisition
- * Investigation
- * Methodology
- * Project administration
- * Resources
- * Software
- * Supervision
- * Validation
- * Visualization
- * Writing – original draft
- * Writing – review and editing

Not all CRediT roles will apply to every manuscript and some authors may contribute through multiple roles. We advise you to read more about CRediT and view an example of a CRediT author statement.

Appendices

We ask you to use the following format for appendices:

- * Identify individual appendices within your article using the format: A, B, etc.
- * Give separate numbering to formulae and equations within appendices using formats such as Eq. (A.1), Eq. (A.2), etc. and in subsequent appendices, Eq. (B.1), Eq. (B. 2) etc. In a similar way, give separate numbering to tables and figures using formats such as Table A.1; Fig. A.1, etc.

References

References within text

Any references cited within your article should also be present in your reference list and vice versa. Some guidelines:

- * References cited in your abstract must be given in full.

- We recommend that you do not include unpublished results and personal communications in your reference list, though you may mention them in the text of your article.
- Any unpublished results and personal communications included in your reference list must follow the standard reference style of the journal. In substitution of the publication date add "unpublished results" or "personal communication."

References cited as "in press" imply that the item has been accepted for publication.

Linking to cited sources will increase the discoverability of your research. We encourage the use of Digital Object Identifiers (DOIs) as reference links, as they provide a permanent link to the electronic article referenced.

Before submission, check that all data provided in your reference list are correct, including any references which have been copied. Providing correct reference data allows us to link to abstracting and indexing services such as Scopus, Crossref and PubMed. Any incorrect surnames, journal or book titles, publication years or pagination within your references may prevent link creation.

Reference style

Indicate references by number(s) in square brackets in line in the text. You can refer to author names within your text, but you must always give the reference number, e.g., "as demonstrated [3,6]. Barnaby and Jones [8] obtained a different result".

Number the references in the reference list in the order in which they appear in the text.

Please note the shortened form for last page number. e.g., 51-9, and that for more than 6 authors the first 6 should be listed followed by 'et al.'.

For further details you are referred to 'Uniform Requirements for Manuscripts submitted to Biomedical Journals' (J Am Med Assoc 1997;277:927-34) and more samples of formatted references.

Abbreviate journal names according to the List of Title Word Abbreviations (LTWA). Examples:

Reference to a journal publication:

6 Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. J Sci Commun 2020;163:51-9. <https://doi.org/10.1016/j.sc.2020.00372>.

Reference to a journal publication with an article number:

7 Van der Geer J, Hanraads JAJ, Lupton RA. The art of writing a scientific article. Heliyon. 2022;19:e00205. <https://doi.org/10.1016/j.heliyon.2022.e00205>.

Reference to a book:

8 Strunk Jr W, White EB. The elements of style. 4th ed. New York: Longman; 2000.

Reference to a chapter in a book:

9 Mettam GR, Adams LB. How to prepare an electronic version of your article. In: Jones BS, Smith RZ, editors. Introduction to the electronic age, New York: E-Publishing Inc; 2023, p. 281-304.

Reference to a website:

10 Cancer Research UK. Cancer statistics reports for the UK, <http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/>; 2023 [accessed 13 March 2023].

Reference to a dataset:

11 Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions [dataset]. Mendeley Data. 2015. <https://doi.org/10.17632/xwj98nb39r.1>.

Reference to software:

12 Coon E, Berndt M, Jan A, Svyatsky D, Atchley A, Kikinzon E, et al. Advanced Terrestrial Simulator (ATS). Version 0.88 [software]. Zenodo; 2020 Mar 25. <https://doi.org/10.5281/zenodo.3727209>.

Web references

When listing web references, as a minimum you should provide the full URL and the date when the reference was last accessed. Additional information (e.g. DOI, author names, dates or reference to a source publication) should also be provided, if known.

You can list web references separately under a new heading directly after your reference list or include them in your reference list.

Data references

We encourage you to cite underlying or relevant datasets within article text and to list data references in the reference list. When citing data

references, you should include:

- author name(s)
- dataset title
- data repository
- version (where available)
- year
- global persistent identifier

Add [dataset] immediately before your reference. This will help us to properly identify the dataset. The [dataset] identifier will not appear in your published article.

Preprint references

We ask you to mark preprints clearly. You should include the word "preprint" or the name of the preprint server as part of your reference and provide the preprint DOI.

Where a preprint has subsequently become available as a peer-reviewed publication, use the formal publication as your reference.

If there are preprints that are central to your work or that cover crucial developments in the topic, but they are not yet formally published, you may reference the preprint.

Reference management software

Most Elsevier journals have their reference template available in popular reference management software products. These include products that support Citation Style Language (CSL) such as Mendeley Reference Manager.

If you use a citation plug-in from these products, select the relevant journal template and all your citations and bibliographies will automatically be formatted in the journal style. We advise you to remove all field codes before submitting your manuscript to any reference management software product.

If a template is not available for this journal, follow the format given in examples in the reference style section of this Guide for Authors.

Submitting your manuscript

Submission checklist

Before completing the submission of your manuscript, we advise you to read our submission checklist:

- One author has been designated as the corresponding author and their full contact details (email address, full postal address, and phone numbers) have been provided. Only the corresponding author's affiliation will be used to determine eligibility for the publishing agreement.

Continua

- All files have been uploaded, including tables and figures (including titles, captions, and footnotes), keywords, supplementary materials, and videos.
- Spelling and grammar checks have been carried out.
- All references in the article text are cited in the reference list, and vice versa.
- Permission has been obtained for the use of any copyrighted material from other sources, including the Web.
- For open access articles, all authors understand that they are responsible for payment of the article publishing charge (APC) if the manuscript is accepted. Payment of the APC may be covered by the corresponding author's institution, or the research funder.

Submit online

Our online submission system guides you through the process steps of entering your manuscript details and uploading your files. The system converts your article files to a single PDF file used in the peer-review process.

Editable files (e.g., Word, LaTeX) are required to typeset your article for final publication. All correspondence, including notification of the editor's decision and requests for revision, is sent by email.

Please follow this link to submit your paper.

After receiving a final decision

Article Transfer Service

If your manuscript is more suitable for an alternative journal published by Elsevier, you may receive an email asking you to consider transferring your manuscript via the Elsevier Article Transfer Service.

The recommendation could come from the journal editor, a dedicated in-house scientific managing editor, a tool-assisted recommendation or a combination.

If you agree with the recommendation, your manuscript will be transferred and independently reviewed by the editors of the new journal. You will have the opportunity to make revisions, if necessary, before the submission is complete at the destination journal.

Publishing agreement

Authors will be asked to complete a publishing agreement after acceptance. The corresponding author will receive a link to the online agreement by email. We advise you to read Elsevier's policies related to copyright to learn more about our copyright policies and your, and your employer's/institution's, additional rights for subscription and open access articles.

License options

Authors will be offered open access user license options which will determine how you, and third parties, can reuse your open access article. We advise that you review these options and any funding body license requirements before selecting a license option.

Open access

We refer you to our open access information page to learn about open access options for this journal.

Permission for copyrighted works

If excerpts from other copyrighted works are included in your article, you must obtain written permission from the copyright owners and credit the source(s) within your article using Elsevier's permission request and license form.

Proof correction

To ensure a fast publication process we will ask you to provide proof corrections within two days.

Corresponding authors will be sent an email which includes a link to our online proofing system, allowing annotation and correction of proofs online. The environment is similar to Word. You can edit text, comment on figures and tables and answer questions raised by our copy editor. Our web-based proofing service ensures a faster and less error-prone process.

You can choose to annotate and upload your edits on the PDF version of your article, if preferred. We will provide you with proofing instructions and available alternative proofing methods in our email.

The purpose of the proof is to check the typesetting, editing, completeness and correctness of your article text, tables and figures. Significant changes to your article at the proofing stage will only be considered with approval of the journal editor.

Share Link

A customized Share Link, providing 50 days free access to the final published version of your article on ScienceDirect, will be sent by email to the corresponding author. The Share Link can be used to share your article on any communication channel, such as by email or on social media.

A Share Link will not be provided if your article is published open access. The final published version of your open access article will be openly available on ScienceDirect and can be shared through the article DOI link.

Responsible sharing

We encourage you to share and promote your article to give additional visibility to your work, enabling your paper to contribute to scientific progress and foster the exchange of scientific developments within your field. Read more about how to responsibly share and promote your article.

Resources for authors

Elsevier Researcher Academy

If you would like help to improve your submission or navigate the publication process, support is available via Elsevier Researcher Academy.

Elsevier Researcher Academy offers free e-learning modules, webinars, downloadable guides and research writing and peer review process resources.

Language and editing services

We recommend that you write in American or British English but not a combination of both.

If you feel the English language in your manuscript requires editing to eliminate possible grammatical or spelling errors and to conform to correct scientific English, you may wish to use the English Language Editing service provided by Elsevier's Author Services.

Getting help and support

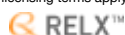
Author support

We recommend that you visit our Journal Article Publishing Support Center if you have questions about the editorial process or require technical support for your submission. Some popular FAQs:

- How can I track the status of my submitted article?
- When will my article be published?



All content on this site: Copyright © 2026 Elsevier B.V., its licensors, and contributors. All rights are reserved, including those for text and data mining, AI training, and similar technologies. For all open access content, the relevant licensing terms apply.



Fonte: ELSEVIER. Guide for Authors. 2026. Disponível em:

<https://www.sciencedirect.com/journal/epilepsy-and-behavior/publish/guide-for-authors>

Vagus Nerve Stimulation in Pediatric Patients with Lennox–Gastaut Syndrome: A Systematic Review

João Cândido Spezia de Souza^{1*}, MS; Marina Ilha Zimmermann¹, MS; Natan Lucca Lima¹, MS; Maruí Weber Corseuil Giehl², PhD; Ana Carolina Lobor Cancelier², MD, PhD.

Affiliations

¹ Faculty of Medicine, Federal University of Santa Catarina (UFSC), Araranguá, Santa Catarina, Brazil.

² Department of Medical Sciences, Federal University of Santa Catarina (UFSC), Araranguá, Santa Catarina, Brazil.

Corresponding Author

João Cândido Spezia de Souza; Faculty of Medicine, Federal University of Santa Catarina (UFSC), Araranguá, Santa Catarina, Brazil. R. Gov. Jorge Lacerda, 3201, 88906-072

E-mail joao.spezia@grad.ufsc.br

Phone: +55 47 99211-2039

Abstract

Background: This study evaluates the efficacy and safety of Vagus Nerve Stimulation (VNS) in the treatment of refractory Lennox–Gastaut Syndrome (LGS) in pediatric patients. **Methods:** A systematic literature review was conducted based on observational studies and case series analyses, followed by assessment of risk of bias using the ROBINS-I tool. **Results:** The results demonstrated that, among the combined sample of 456 patients included in the selected studies, 374 achieved a reduction greater than 50% in seizure frequency after VNS therapy, with some cases reporting complete seizure remission. The analysis suggests greater effectiveness for atonic seizures (drop attacks), followed by tonic and absence seizures. Regarding secondary outcomes, significant qualitative improvements were reported in alertness, attention, and sleep quality. Although the intervention appears to be relatively safe, the included studies presented a high risk of bias in the outcome measurement domain, mainly due to the impracticality of blinding in surgical procedures and the subjective nature of caregiver-reported outcomes. The heterogeneity of clinical responses appears to be associated with differences in stimulation parameters and variability in baseline clinical conditions. **Conclusion:** Overall, VNS demonstrated findings suggestive of potential utility in the management of LGS; however, randomized clinical trials with larger syndrome-specific samples and standardized stimulation protocols are still required.

Keywords: Pediatrics; Epilepsy; Epileptic Syndromes; Lennox–Gastaut Syndrome; Neuromodulation; Vagus Nerve Stimulation.

INTRODUCTION

Childhood epilepsies constitute one of the most common chronic neurological conditions during this stage of life and, in many cases, present a relatively favorable course. However, Lennox-Gastaut syndrome (LGS) contrasts with this pattern, as it is a severe epileptic encephalopathy with a significant impact on child development [1].

Lennox-Gastaut syndrome is a pediatric condition characterized by multiple seizure types, frequently resistant to pharmacological treatment, with specific electroencephalographic (EEG) patterns, such as slow spike-and-wave complexes or generalized paroxysmal fast activity, additionally associated with intellectual disability [2].

The prevalence of Lennox-Gastaut encephalopathy is estimated at 1 to 2% of all patients with epilepsy [2]. Its etiology is heterogeneous and may involve genetic, structural, or metabolic causes, responsible for approximately 65 to 75% of cases; in the remaining cases, the cause remains unknown [2].

Although symptom onset occurs predominantly during childhood, LGS has lifelong repercussions, since seizures tend to persist in a refractory manner and may be associated with cognitive sequelae, such as intellectual and functional disability, in addition to behavioral problems [3]. A retrospective cohort study that followed 38 adults with childhood-diagnosed LGS reported that all patients experienced three or more types of epileptic seizures throughout their clinical history, including atypical absences, tonic seizures, generalized tonic-clonic seizures, focal seizures, and myoclonic seizures, all resistant to medication [3].

Given the refractoriness to pharmacological treatment, the literature describes different non-pharmacological therapeutic alternatives for the control of LGS [4–10]. The main interventions include corpus callosotomy, vagus nerve stimulation (VNS), and the ketogenic diet. Corpus callosotomy has demonstrated greater efficacy than the ketogenic diet in reducing seizure frequency in patients with LGS [11]. However, it is a surgical procedure frequently associated with adverse effects, especially in the immediate postoperative period [11,12]. In contrast, VNS has been associated with improvements in alertness and quality of life, in addition to presenting a predominantly favorable safety profile, with a lower occurrence of severe complications when compared to corpus callosotomy [12–14].

VNS consists of the surgical implantation of a device that promotes intermittent electrical stimulation of the vagus nerve, aiming to modulate neuronal activity and, consequently, reduce the frequency, intensity, and severity of epileptic seizures [15,16]. The device, generally implanted in the thoracic region, is connected to the vagus nerve in the cervical region and functions by delivering electrical pulses at regular intervals, contributing to the control of abnormal electrical discharges in

the brain [15,17,18]. Recent studies have demonstrated that VNS appears to be effective in patients with LGS, with response rates defined as a reduction equal to or greater than 50% in seizure frequency, ranging from 54% to 66.7% in different analyses [16,19].

Despite the increasing use of VNS, there are still gaps regarding the magnitude of its benefit specifically in pediatric patients with LGS. In this context, this systematic review aimed to evaluate the effectiveness of VNS in reducing epileptic seizures in patients with LGS, considering seizure frequency, seizure type, and post-intervention symptom evolution. Additionally, the study sought to analyze the occurrence of adverse effects and the tolerability of VNS in children and adolescents with LGS.

METHODOLOGY

This systematic literature review was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations and registered in the PROSPERO systematic review database (CRD420251151322).

2.1 ELIGIBILITY CRITERIA

Although Randomized Clinical Trials (RCTs) were eligible, no study with this design met the established criteria; therefore, cohort and case series studies conducted in children older than one month but younger than 18 years diagnosed with LGS and who underwent VNS were included. Studies were required to present data regarding epileptic seizures and the occurrence of adverse events. Duplicated studies, publications primarily focused on other epileptic syndromes, narrative reviews, editorials, experimental animal studies, as well as publications without full-text access were excluded.

2.2 SEARCH STRATEGY

The following databases were used: MEDLINE (via PubMed), Embase, Cochrane Library, and Web of Science, without language restrictions.

For the documentary search, the selected descriptors were based on the Medical Subject Headings (MeSH). The search strategy was adapted to the specificities of each database. The keywords used in MEDLINE were as follows: (Child OR children OR pediatric OR infant OR childhood) AND (Gastaut OR LGS) AND vagus.

2.3 DATA SELECTION, EXTRACTION, SYNTHESIS, AND ANALYSIS

Applying the PRISMA methodology through the PICOS strategy, the following parameters were defined: a population composed of children aged 1 month to 18 years with a confirmed diagnosis of Lennox-Gastaut Syndrome (LGS), according to the International League Against

Epilepsy (ILAE) criteria, characterized by multiple seizures, electroencephalogram (EEG) with a slow spike-and-wave pattern, and cognitive impairment; intervention based on vagus nerve stimulation; comparison with pharmacological treatment, ketogenic diet, and surgical approaches other than vagus nerve stimulation (VNS); outcomes related to clinical response, reduction in seizure frequency, and reduction in the rate of adverse effects; and, finally, inclusion of studies with randomized clinical trial (RCT), prospective cohort, and case series designs.

Article selection was performed using the strategy described above, and data extraction was independently conducted by the two authors (JCSS and MIZ). Occasional disagreements were resolved through consensus between peers and supervisors. The Zotero software was used for manual bibliography selection, identification and exclusion of duplicate material, organization and review of titles and abstracts, as well as reference management.

The studies were screened to verify eligibility criteria and were included in the systematic review when they met the inclusion and exclusion criteria. The presentation of the study screening process was illustrated by the PRISMA flowchart (Figure 1).

2.4 RISK OF BIAS ASSESSMENT

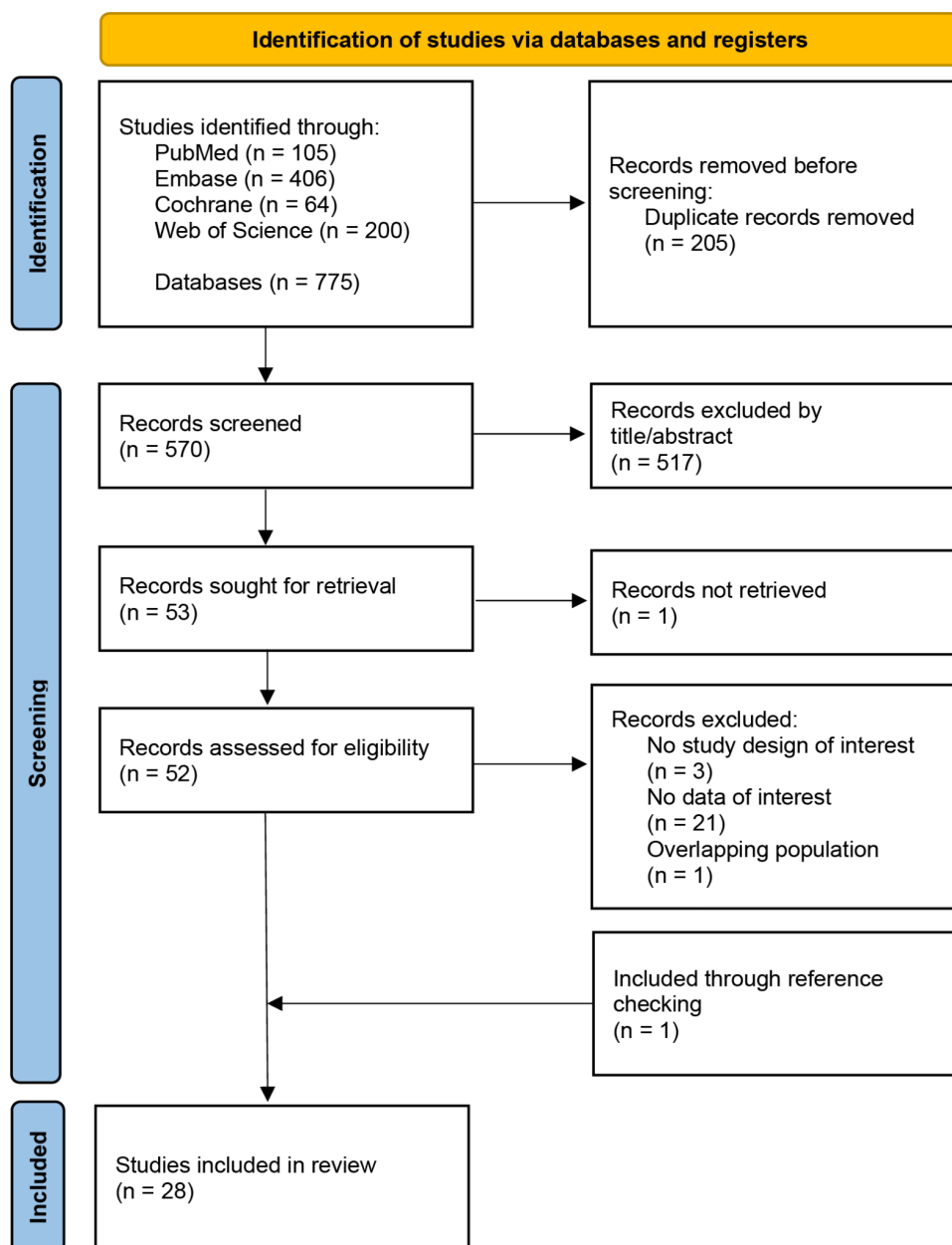
The risk of bias assessment was conducted using the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool, corresponding to the studies included after the screening stage. The tool assesses the risk of bias across different domains, including bias due to confounding, participant selection, classification of interventions, missing data, outcome measurement, and selection of reported results. According to the ROBINS-I criteria, the studies were classified as presenting low, moderate, serious, or critical risk of bias. As this is a domain-based judgment assessment, the tool does not use numerical scoring, and the overall study classification is determined by the domain with the highest risk.

RESULTS

3.1 STUDY SELECTION

The search across the four databases identified 775 references, of which 205 were removed for being duplicates and 517 were included for meeting the pre-established inclusion criteria. Of these references, only one did not allow access to the full text and was therefore excluded. The remaining studies proceeded to full-text reading, and at this stage, three were excluded for not having the design of interest, twenty-one for containing data different from those sought, and one due to overlapping population. In addition, one article was included through reference checking. Thus, twenty-eight references were included in this review for meeting all established criteria, as illustrated by the PRISMA flowchart presented in Figure 1.

Figure 1. PRISMA Flowchart



3.2 STUDY CHARACTERISTICS

Among the selected articles, 15 were retrospective cohort studies based on medical record review, seven were prospective cohort studies, and six were case series.

It is important to highlight that case series were not initially considered a mandatory inclusion criterion. However, studies with this design were also deemed eligible provided they included at least one patient with LGS younger than 18 years of age at the time of VNS implantation. In some articles, although the total sample was larger, the specific number of patients with LGS was small. Nevertheless, these studies were retained in the analysis, and only the data referring to these patients were considered.

Across the primary studies, a total of 456 individuals were included, with sample sizes ranging from 1 to 146. The age range at the time of VNS implantation varied from one month of life to 18 years. Table 1 presents, for each study, the study design, sample size, age at electrode insertion, time between surgery and initiation of electrical stimulation, initial current and frequency parameters, stimulation and rest times (on/off), primary and secondary outcomes, adverse events, and follow-up duration for each study.

Table 1. General data of the selected articles

Author, Year	Study Design	Sample	Age at onset of epileptic seizures (months), mean $\pm$ standard deviation	Age at implantation (months), mean $\pm$ standard deviation.	Time to electrode activation after surgery (in days)	Initial electrode current (mA)	Frequency (Hz)	Time ON(s)//O FF(min)	Primary outcome	Secondary outcome	Adverse effects	Follow up (months)
Abdelmouty, 2021 [20]	CR	71	18	20,82	NA	NA	NA	NA	NC	SO, AT, AL	I, D, PR, MV, O	24
Alanazi, 2022 [21]	CR	4	18,8 $\pm$ 20,5	11,7 $\pm$ 3,3	7 - 15	0,25	NA	30//5	NC	NA	DI	48
Bremer, 2006 [22]	CR	11	NA	NA	NA	NA	NA	30//5	NC, QC	AL	Death	36
Buoni, 2004 [23]	SC	5	33 $\pm$ 39,4	199,2 $\pm$ 18,2	14	0,25	NA	25,4 $\pm$ 10,3 ; 3,25 $\pm$ 2,42	NC, QC	AL, CO	C	36
Cukiert, 2013 [24]	CP	14	NA	NA	21	0,25	30	30//5	QC	HM	R	NA
Cukiert, 2024 [25]	CR	19	NA	86,4	NA	NA	NA	NA	NC	NA	NA	48
Elliott, 2011 [26]	CR	11	NA	NA	NA	NA	NA	NA	NC	NA	NA	>3
Fang, 2020 [27]	CR	NA	NA	NA	NA	0,25	30	30//5	NC	NA	NA	24
Flesler,	CR	88	NA	NA	14 a 21 days	0,25	20-30	30//1,1-5	NC, QC	NA	NA	24

2017 [28]												
Frost, 2001 [29]	CR	50	NA	NA	NA	0,25	30	30//5	NC, QC	AL/AT, CO	I, D, R, T, PC, PR, S	6
Hallböök, 2005 [30]	CP	4	18 ± 28	NA	NA	0,25	30	30//5	NC, QC	NA	NA	9
Hentati, 2013 [31]	CR	3	NA	96	NA	NA	NA	30//5	NC	NA	NA	18 (mean)
Hosain, 2000 [32]	SC	8	NA	142,5 ± 47,8	NA	0,75	NA	30//5	NC	NA	NA	6
Katagiri, 2016 [33]	CR	8	14,8 ± 13,15	87 ± 43,85	14 a 21	0,25	NA	30//5	NC	NA	R	60
Kruse, 2010 [34]	SC	1	60 ± 0	132 ± 0	NA	2,5	NA	30//5	NC, QC	CO	NA	43,2
Lagae, 2012 [35]	CR	20	NA	NA	NA	2	25	30//5	NC	NA	NA	>6
Lundgren, 1998 [36]	SC	3	5 ± 1	76 ± 30,2	1 a 5	0,25	30	30//5	NC	NA	S, A	18
Majoie, 2005 [37]	CP	12	23,33 ± 29,06	129,45 ± 38,1	1	0,25	NA	30//3	NC, QC	NA	NA	24
Mikati, 2009 [38]	CR	2	72 ± 16,97	174 ± 59,4	7 a 14	0,25	30	30//5	NC	CO	NA	27
Orosz, 2014 [39]	CR	146	NA	NA	NA	NA	NA	NA	NC	NA	NA	24
Parker, 1999 [40]	CP	9	12,4 ± 14,09	133,1 ± 37,8	NA	0,25	NA	30//6	NC	NA	I	24
Preto												
Mimura, 2017 [41]	SC	1	0 ± 0	120 ± 0	NA	NA	NA	NA	NC, QC	RM	NA	24
Rossignol, 2009 [42]	CP	5	27,2 ± 16,89	NA	NA	0,25	NA	NA	NC, QC	NA	DI, Death	24
Rychlicki, 2006 [43]	CP	9	NA	133,2 ± NA	NA	0,5	30	30//5	NC	NA	NA	36
Shahwan, 2009 [18]	CR	9	NA	126,72 ± 39,6	NA	0,25	30	30//3	NC, QC	NA	AP	102
Tekin, 2017 [44]	CP	3	48 ± 24	128 ± 38,6	NA	NA	NA	NA	NC, QC	NA	NA	34
Tormasiov a, 2014 [45]	SC	1	NA	84 ± 0	0	0,25	20	30//3	NC	HM	NA	36
Zamponi, 2011 [46]	CR	10	NA	134,76 ± 41,37	NA	NA	NA	NA	NC, QC	NA	NA	12

Legend: A - Asthenia, AL - Alertness, AP - Psychomotor agitation, AT - Attention, C - Headache, CO - Communication (verbal and social), CP - Prospective cohort, CR - Retrospective cohort, D - Pain, DI - Dysphagia, HM - Honeymoon, I - Infection, MV - Voice changes, NA - Not available, NC - Number of seizures, O - Other, PC - Cervical paresthesia, PR - Respiratory problems, QC - Seizure quality, R - Hoarseness, RM - Medication reduction, S - Sialorrhea, SC - Case series, SL - Sleep, T - Cough.

Regarding the time to electrode activation after surgery, most studies did not provide this information; however, when reported, it ranged from 7 to 21 days, with

activation performed once adequate healing, absence of local infectious signs, and the specific protocols of each study were confirmed.

The vagus nerve stimulation parameters also followed the particularities of each center. An initial current of 0.25 mA was selected in 53.5% of the included studies; however, some centers opted to initiate stimulation at 0.5 mA or 0.75 mA. Nevertheless, the electrical current was progressively increased according to each study protocol or according to the individual tolerance of the patients. The stimulation frequency reported in the studies ranged from 20 to 30 Hz, with progression depending on patient tolerance and the individual protocols of each center.

The on-off time corresponds to the cyclic period during which vagal stimulation occurs, followed by the period during which stimulation is turned off and therefore absent. A stimulation time of 30 s was used in 67.8% of the selected studies and was nearly unanimous when this parameter was reported. In contrast, the off-time ranged from 2 to approximately 10 minutes, with no consensus regarding the ideal duration.

Follow-up duration was also a heterogeneous variable, ranging from 3 to 102 months.

3.3 RISK OF BIAS ASSESSMENT OF THE STUDIES

All studies included in this review had an observational design and were assessed using the ROBINS-I tool. The study by Alanazi et al. [21] was the only one to incorporate a comparison group between VNS and another intervention and was classified as having a critical risk of bias, mainly due to limitations in the confounding domain (D1).

Regarding the overall classification, 6 of the 28 studies (21.4%) were categorized as having a critical risk of bias — Abdelmoity et al. [20], Alanazi et al. [21], Bremer et al. [22], Fang et al. [27], Kruse et. al [34], and Tormasiova et. al [45]. The remaining 22 studies (78.6%) were classified as having a serious risk of bias, and no study was identified as having low or moderate risk of bias. The detailed distribution of risk of bias across domains, as well as the individual assessment of each study, is presented in Figure 2.

Figure 2. Risk of Bias

	Risk of bias						Overall
	D1	D2	D3	D4	D5	D6	
Abdelmoity, 2021	●	+	+	●	×	-	●
Alanazi, 2022	●	+	+	+	×	-	●
Bremer, 2006	●	+	×	×	×	-	●
Buoni, 2004	●	+	-	+	×	-	×
Cukiert, 2013	●	+	+	+	×	+	×
Cukiert, 2024	●	+	-	+	×	-	×
Elliott, 2011	●	+	+	+	×	-	×
Fang, 2020	●	+	+	●	×	×	●
Flesler, 2017	●	+	+	+	×	-	×
Frost, 2001	●	+	+	+	×	-	×
Hallböök, 2005	●	+	+	+	×	-	×
Hentati, 2013	●	+	+	+	×	-	×
Hosain, 2000	●	+	-	+	×	×	×
Katagiri, 2016	●	+	-	+	×	-	×
Kruse, 2010	●	+	×	-	×	×	●
Lagae, 2012	●	+	+	+	×	-	×
Lundgren, 1998	●	+	+	+	×	-	×
Majoie, 2005	●	+	+	+	×	-	×
Mikati, 2009	●	+	-	+	×	-	×
Orosz, 2014	●	+	+	×	×	-	×
Parker, 1999	●	+	+	+	×	-	×
Preto Mimura, 2017	●	+	-	-	×	-	×
Rosignol, 2009	●	+	+	+	×	-	×
Rychlicki, 2006	●	+	+	+	×	-	×
Shawan, 2009	●	+	+	+	×	-	×
Tekin, 2017	●	+	+	+	×	-	×
Tormasiova, 2014	●	+	×	+	×	-	×
Zamponi, 2011	●	+	+	+	×	-	×

D1: Bias due to confounding
 D2: Bias in classification of interventions
 D3: Bias in selection of participants
 D4: Bias due to missing data
 D5: Bias arising from measurement of the outcome
 D6: Bias in selection of the reported result

Judgement
 ● Critical
 ● Serious
 ● Moderate
 ● Low
 ● Not applicable

3.4 PRIMARY OUTCOMES

Two parameters were considered primary outcomes: the number of epileptic seizures and seizure characteristics after the intervention. The vast majority of the articles (96.4%) reported seizure frequency in their results; however, only 42.8% described seizure type after VNS.

3.4.1 VARIATION IN SEIZURE FREQUENCY AFTER VNS

3.4.1.1 OVERVIEW OF THE SAMPLE AND RESPONSE CATEGORIZATION

The analysis of the efficacy of Vagus Nerve Stimulation (VNS) in reducing seizure frequency demonstrated marked methodological heterogeneity among the included studies. To minimize this variability and allow greater comparability among findings, outcomes were stratified according to post-implant follow-up duration, encompassing early (1–6 months), intermediate, and long-term (>24 months) evaluations. Studies with follow-up periods that could be standardized were systematized in Table 2.

Treatment response was predominantly defined based on the proportion of patients who achieved reductions of $\geq 50\%$ or $\geq 75\%$ in seizure frequency, complemented by the identification of seizure-free patients, those with no observed change, and those who experienced clinical worsening.

Studies that employed global response metrics or did not present standardized follow-up periods were grouped into a specific analytical category, and their results were descriptively synthesized according to overall efficacy trends.

Table 2. Results related to the number of seizures of all types after VNS

Author, Year	Sample	Increase in the number of seizures, n (%)	Increase in the number of seizures, n (%)	Reduction of <50% in the number of seizures, n (%)	Reduction of >50% in the number of seizures, n (%)	Reduction of >75% in the number of seizures, n (%)	Seizure-free
1 month after VNS							
Abdelmoity , 2021 [20]	26	4 (15%)	7 (27%)	5 (19%)	4 (15%)	3 (12%)	3 (12%)
Frost, 2001 [29]	46	1 (2%)	-	-	20 (43%)	7 (15%)	-
3 month after VNS							
Abdelmoity , 2021 [20]	32	4 (13%)	10 (31%)	4 (13%)	8 (25%)	3 (9%)	3 (9%)
Frost, 2001 [29]	43	3 (7%)	-	-	24 (56%)	15 (35%)	-
6 months after VNS							
Abdelmoity , 2021 [20]	44	3 (7%)	9 (21%)	8 (18%)	8 (18%)	11 (25%)	5 (11%)
Frost, 2001 [29]	24	-	-	-	14 (58%)	9 (37%)	-
Hosain, 2000 [32]	8	-	1 (12,5%)	3 (37,5%)	1 (12,5%)	3 (37,5%)	-
Orosz, 2014 [39]	123	-	-	-	35 (28%)	-	-

[illegible]

Abdelmoity

, 2021 [20]	24	5 (21%)	1 (4%)	2 (8%)	1 (4%)	10 (42%)	5 (21%)
Shahwan, 2009 [18]	9	-	2 (22%)	-	1 (11%)	5 (55%)	1 (11%)

≥24 months after VNS**Abdelmoity**

, 2021 [20]	23	3 (13%)	1 (4%)	4 (17%)	4 (17%)	7 (30%)	4 (17%)
Flesler, 2017 [28]	88	-	-	-	71 (81%)	-	-
Kruse, 2010 [34]	1	-	-	-	1 (100%)	-	-
Mikati, 2009 [38]	1	-	-	-	1 (100%)	-	-
Orosz, 2014 [39]	87	-	-	-	34 (39%)	-	-
Rossignol, 2009 [42]	5	-	2 (40%)	-	2 (40%)	-	1 (20%)
Tekin, 2017 [44]	3	-	2 (66%)	1 (33%)	-	-	-

3.4.1.2 SHORT-TERM RESULTS (1 TO 6 MONTHS POST-VNS)

During the first months after device implantation, marked variability in therapeutic response was observed among the studies, reflecting differences in sample characteristics and methodological designs. In the first month of follow-up, the cohort reported by Abdelmoity et al. [20] demonstrated an still incipient response, with 27% of patients showing no change in seizure frequency and 15% presenting clinical worsening. Nevertheless, a proportion of patients already exhibited early benefit, with 12% achieving >50% reduction and another 12% >75% reduction. In contrast, Frost et al. [29] reported a more expressive initial response, with 43% of patients achieving >50% reduction during this same period.

At three months, an overall trend toward increased efficacy was observed. In the study by Frost et al. [29], the proportion of responders increased to 56% with >50% reduction and 35% with >75% reduction, indicating progression of the therapeutic effect over time. Conversely, Rychlicki et al. [43] observed a mean overall reduction of only 8% in seizure frequency during the same interval, demonstrating that the magnitude of the initial response may remain limited in certain cohorts.

At six months of follow-up, the effects of neuromodulation became more consistent in most studies. Frost et al. [29] maintained high response rates, with 58% of patients presenting >50% reduction and 37% >75% reduction. In the largest cohort, Orosz et al. [39] 28% of patients achieved >50% reduction. Similarly, Fang et al. [27], when specifically evaluating patients with Lennox–Gastaut Syndrome, observed a mean reduction of 73.1% in seizure frequency at 24 months. Results of lower magnitude were described by Parker et al. [40], in which, during the 0–6 month interval, 55% of patients remained with <50% reduction, although 33% already exhibited >50% response, with one case of clinical worsening.

Isolated cases of marked early response were also described, such as in the study by Tormasiova et al. [45], which reported a seizure-free patient as early as the fourth month post-implantation; however, this outcome was not maintained in subsequent evaluations. Taken together, these findings suggest that, although clinical benefits may be observed early, the response to vagus nerve stimulation tends to progressively intensify during the first months after implantation, with considerable heterogeneity across studies.

3.4.1.3 MID-TERM RESULTS (9 TO 12 MONTHS POST-VNS)

At mid-term follow-up, seizure control rates tended to remain stable or to follow an upward trajectory in most studies. At 12 months, Orosz et al. [39] reported that 33% of patients achieved >50% reduction in seizure frequency. Consistently, Abdelmoity et al. [20] observed expressive results at the same time point, with 32% of patients achieving >50% reduction, 30% >75% reduction, and 11% becoming seizure-free.

The favorable evolution throughout the first year was also described by Parker et al. [40]. During the 6–12 month interval, the proportion of responders ($\geq 50\%$) increased to 5/9 patients, including one case of excellent response ($\geq 90\%$). However, a concomitant increase in the proportion of patients with clinical worsening (3/9) was also observed, highlighting the interindividual variability in response. Similarly, Rychlicki et al. [43] demonstrated gradual progression in efficacy, with the mean reduction in seizure frequency increasing from 3% at the sixth month to 33% at the end of 12 months.

In contrast to this predominantly positive trend, Lundgren et al. [36] identified no significant clinical gain during the 10–12 month period in a small sample ($n=3$), in which no patient exceeded 80% reduction and clinical stability predominated (2/3). Collectively, the results suggest that the efficacy of the intervention tends to consolidate over the first year, although with substantial variability across studies, including the presence of subgroups with limited response, absence of measurable clinical benefit, or even worsening of seizures.

3.4.1.4 LONG-TERM RESULTS (>12 TO ≥24 MONTHS POST-VNS)

The analysis of follow-up periods longer than 12 months reinforces the progressive and cumulative nature of VNS efficacy among responder patients. Within this interval, Cukiert et al. [25] and Lagae et al. [35] reported high proportions of clinical response, with 79% and 60% of their respective samples achieving >50% reduction in seizure frequency. Additionally, Bremer et al. [22] described a clinically relevant finding in which 27% of patients became specifically free from atonic seizures, suggesting a potentially differentiated effect of VNS on seizure subtypes with greater functional impact.

At approximately 18 months of follow-up, Abdelmoity et al. [20] demonstrated a predominance of robust responses, with 42% of patients presenting >75% reduction and 21% achieving complete seizure remission. In agreement, the longitudinal data from Rychlicki et al. [43] demonstrated maintenance and progression of efficacy over time, with a mean reduction in seizure frequency of 45% at 18 months, reaching 50% at 24 months, followed by a slight decrease to 31% after three years of follow-up.

In studies with follow-up equal to or greater than 24 months, consolidation of therapeutic benefit was observed in a significant proportion of cohorts. Flesler et al. [28] reported one of the highest response rates, with 81% of patients achieving >50% reduction. More moderate results were described by Orosz et al. [39], with 39% of individuals within this same response range. Abdelmoity et al. [20] demonstrated maintenance of expressive long-term responses, with 30% of patients presenting >75% reduction and 17% remaining seizure-free.

Despite these favorable findings, some studies point to the possibility of loss of efficacy over time. In this context, Tormasiova et al. [45] described a case of initial complete response that was not sustained, with seizure frequency returning to baseline levels after three years of follow-up, suggesting the potential occurrence of tolerance or attenuation of the therapeutic effect in isolated cases.

3.4.1.5 VARIABLE OUTCOMES AND INDEPENDENT FINDINGS

Beyond analyses stratified by follow-up duration, some studies reported their results using global response metrics or with emphasis on unfavorable outcomes, broadening the understanding of the spectrum of intervention effects. In this context, Elliott et al. [26] observed an overall reduction of 51%, whereas Hentati et al. [31] reported a more modest median reduction (23%), highlighting variability in magnitude among different samples. At the individual level, Preto Mimura et al. [41] documented a case with marked clinical response, characterized by an absolute reduction in seizure frequency from seven to two daily events.

Conversely, the data also demonstrate a non-negligible occurrence of lack of response or even adverse outcomes. Cukiert et al. [24] reported worsening of seizures in 5 of 14 patients, corresponding to a relevant proportion of non-responders with clinical worsening. Similarly, Majoie et al. [37], in a sample of 12 individuals, observed that 8 did not achieve the >50% reduction threshold, including two cases with increased seizure frequency and one with no change compared to baseline. Furthermore, the late follow-up described by Lundgren et al. [36] (16–18 months) reinforces this response heterogeneity, with equal distribution between clinical worsening and stability (50% each), without records of significant improvement during this interval.

Considering the studies as a whole, these findings indicate that, although VNS demonstrates global clinical benefit in a substantial proportion of patients, the therapeutic response is not uniform, with both variations in effect magnitude and the presence of subgroups with limited response or unfavorable evolution being observed.

3.4.2 RESPONSE ACCORDING TO SEIZURE TYPE AND QUALITY

For the analysis of outcomes related to seizure quality and type, the data were organized according to semiological categories, allowing a more refined evaluation of the response to VNS among different seizure subtypes, as well as qualitative aspects such as intensity and duration of events.

3.4.2.1 ATONIC SEIZURES AND DROP ATTACKS (DA)

Atonic seizures and drop attacks generally demonstrated high responsiveness to VNS, although with variability across cohorts. Bremer et al. [22] observed complete resolution (100%) of this subtype in 3 patients (27%), whereas Buoni et al. [23] reported a 50% reduction in two patients and complete remission in one case. In a larger sample, Flesler et al. [28], composed of patients with LGS, documented a mean reduction of 82% in atonic drop seizures.

Longitudinal data from Frost et al. [29] demonstrated a pattern of progressive response, with median reductions of 47% in the first month, 55% in the third month, and 88% in the sixth month post-implantation. Similarly, Shahwan et al. [18] described abolition of daytime atonic seizures in 5 of 7 patients, with no recurrence of this subtype at the end of follow-up in individuals with LGS. Additional results included a 52.6% reduction in one patient in the study by Hallböök et al. [30] and complete remission after two years in the report by Rosignol et al. [42]. In contrast, Cukiert et al. [24] did not identify statistically significant improvement for atonic seizures in their sample, highlighting the heterogeneity of results.

3.4.2.2 TONIC AND GENERALIZED TONIC–CLONIC SEIZURES

The response of tonic and generalized tonic–clonic seizures was generally favorable, with substantial reductions described in different studies. Flesler et al. [28] reported a 96% reduction in tonic seizures among patients with LGS, whereas Kruse et al. [34] and Cukiert et al. [24] documented a decrease in the frequency of tonic and generalized tonic–clonic seizures.

Shahwan et al. [18] observed complete abolition of tonic seizures during the daytime period, with persistence only of nocturnal or awakening-related events. Rossignol et al. [42] reported >50% reduction in two patients over two years, and Tekin et al. [44] described reduction of generalized tonic seizures with head drop in one case. On the other hand, Cukiert et al. [24] also reported absence of significant improvement in this subtype in part of their cohort, indicating variability in response.

3.4.2.3 ABSENCE AND MYOCLONIC SEIZURES

For absence and myoclonic seizures, the findings suggest a consistent response, frequently with a pattern of progressive improvement. Frost et al. [29] demonstrated median reduction of atypical absences of 48% in the first month, 73% in the third month, and 81% in the sixth month. Flesler et al. [28] reported a 73% reduction in absence seizures, whereas Cukiert et al. [16] described VNS efficacy for both atypical absence and myoclonic seizures.

Hallböök et al. [30] documented complete cessation of myoclonic seizures in one patient; however, intracortical heterogeneity was observed, with another individual presenting a 55.5% reduction in atypical absences but a 100% increase in secondarily generalized seizures. Additional findings from Rossignol et al. and Tekin et al. [44] included cases of complete remission or relevant reduction in myoclonic and myoclonic absence seizures.

3.4.2.4 OTHER SUBTYPES AND QUALITATIVE ASPECTS OF SEIZURES

Regarding other subtypes, Frost et al. [29] reported more modest reductions in complex partial seizures, with decreases of 20% in the first month and 23% in the third month. Hallböök et al. [30] described a sustained 50% reduction in secondarily generalized seizures in one patient after nine months, contrasting with a 33.3% increase in another individual. Majoie et al. [37], in turn, highlighted that although different subtypes presented distinct nominal responses, these differences did not reach statistical significance.

Regarding qualitative outcomes, the data suggest an additional impact of VNS beyond seizure frequency. Preto Mimura et al. [41] reported reduction in the intensity and duration of events, whereas Shahwan et al. [18] described milder seizures, of shorter duration, and associated with faster postictal recovery. These findings indicate that the benefits of VNS may extend to modulation of the clinical severity of seizures, even in cases with limited quantitative reduction.

3.5 SECONDARY OUTCOMES

The analysis of secondary outcomes revealed significant methodological heterogeneity, presenting as abstract variables due to the lack of standardization among the selected references. Each study adopted distinct evaluation criteria, frequently based on non-validated scales or on the subjective perception of caregivers, which limits data uniformity.

Despite this variation, improvement was observed in different aspects of patients' quality of life, mainly manifested by increases in alertness, attention, sleep pattern, and verbal and social communication skills. The honeymoon (HM) phenomenon and reduction of daily pharmacological burden were also noted in some cases.

3.5.1 ALERTNESS, ATTENTION, AND SLEEP

Changes in alertness were longitudinally reported in different studies, with variation throughout follow-up. Abdelmoity et al. [20] documented improvement in alertness in 7/26 patients during the first month, 8/32 in the third month, 22/44 in the sixth month, 12/37 at 12 months, 14/24 at 18 months, and 12/23 at 24 months post-implantation. Consistently, Frost et al. [29] observed improvement in more than 60% of patients at 3 months and in more than 50% at 6 months. Bremer et al. [22] recorded increased alertness in 6/11 patients, with mean onset of effects at approximately 2.5 months, whereas Buoni et al. reported this finding in 1/5 patients.

Similar results were observed in the attention domain. Abdelmoity et al. [20] identified improvement in 7/26 patients during the first month, 8/32 in the third month, 22/44 in the sixth month, 11/37 at 12 months, 14/24 at 18 months, and 12/23 at 24 months, suggesting a temporal pattern comparable to that observed for alertness.

Regarding sleep, Abdelmoity et al. [20] also reported variations over time, with improvement in 5 patients during the first month, 9 in the third month, 19 in the sixth month, 11 at 12 months, 13 at 18 months, and 11 at 24 months, evidencing coexistence of positive responses and absence of effect in subgroups throughout follow-up.

3.5.2 COMMUNICATION, BEHAVIOR, AND SCHOOL PERFORMANCE

Changes in communication and social interaction domains were described in multiple cohorts, although in a less standardized manner. Frost et al. [29] reported that, after 6 months of treatment, at least 25% of patients presented changes in verbal communication and school performance. Buoni et al. [23] observed increased social communication in 20% of patients, whereas Mikati et al. [38] recorded improvement in social aspects in two individuals. In an isolated report, Kruse et al. [34] also described improvement in communication in one patient.

In the behavioral domain, Preto Mimura et al. [41] reported global behavioral improvement. Additional changes included increased appetite, observed by Buoni et al. [23] in 20% of patients.

3.5.3 ADDITIONAL CLINICAL AND THERAPEUTIC PARAMETERS

Among the observed clinical phenomena, the so-called “honeymoon” phenomenon stands out, characterized by transient reduction in seizure frequency before device activation or immediately after implantation. This pattern was described by Cukiert et al. [24] in approximately 85% of patients, as well as by Tormasiova et al. [45].

Additionally, Frost et al. [29] reported improvement in postictal recovery and reduction in seizure clustering in at least 25% of patients after six months of follow-up. In the context of therapeutic management, Preto Mimura et al. [41] described reduction in the number of antiepileptic drugs used, suggesting a potential impact of VNS on optimization of pharmacological treatment.

Globally, the secondary outcomes indicate that the effects of VNS may extend beyond seizure frequency, involving multiple functional domains. However, variability across studies is observed regarding the magnitude and consistency of these findings, as well as limitations related to methodological heterogeneity and the absence of standardization in the measures used.

3.6 ADVERSE EFFECTS

3.6.1 VOICE CHANGES AND RESPIRATORY SYMPTOMS

Events related to phonation and the respiratory tract were the most frequently described among the included studies. Frost et al. [29] reported voice alteration or hoarseness in 22/50 patients, in addition to cough in 15/50 cases. Similar findings were observed by Katagiri et al. [33], with hoarseness in 2/8 patients, and by Cukiert et al. [24], in 1/14 individuals.

During the early postoperative period, Abdelmoity et al. [20] identified the occurrence of adverse effects in 10/26 patients during the first month, including vocal alterations and respiratory symptoms. Episodes of dyspnea were also reported by Frost et al. [29], although at a lower proportion. In general, the studies indicate that these events tend to be transient, with spontaneous resolution over time or after adjustments in stimulation parameters.

3.6.2 SURGICAL SITE COMPLICATIONS AND INFECTIONS

Local complications related to the surgical procedure were described at different frequencies. Abdelmoity et al. [20] reported cases of recurrent infection at the implantation site. Frost et al. [29] recorded local pain in approximately 10% of patients and infection in 4% of the sample. In isolated

situations, infectious events required additional interventions, such as device removal, as described by Parker et al. [40] in one patient.

3.6.3 DYSPHAGIA, SIALORRHEA, AND OTHER SYSTEMIC EVENTS

Adverse events involving swallowing and systemic manifestations were also reported, although at lower frequency. Alanazi et al. [21] described dysphagia in 1/4 patients, whereas Rossignol et al. [42] reported one case of severe dysphagia leading to device removal. Lundgren et al. [36] observed increased salivation in 1/3 patients.

Other events included headache associated with increased stimulation intensity, described by Buoni et al. [23] in one patient (1.25 mA), as well as severe fatigue in 2/3 individuals in the study by Lundgren et al. [36]. Behavioral changes were reported by Shahwan et al. [18] in 2/9 patients, and cervical paresthesia was described by Frost et al. [29]. These findings reflect the diversity of systemic manifestations associated with therapy, generally described in isolation and in small proportions.

3.6.4 RECORDED DEATHS

During follow-up of the included studies, two deaths were recorded. Bremer et al. [22] reported one case of sudden death eight months after implantation, without causal attribution to the VNS device. Rossignol et al. [42] described one death resulting from airway obstruction during feeding, also without a directly established relationship with the intervention.

DISCUSSION

The analysis of the data shows that Vagus Nerve Stimulation (VNS) promotes a progressive therapeutic response, in which the reduction in seizure frequency tends to consolidate and intensify over the first year of follow-up. This observation is corroborated by the American Academy of Neurology (AAN) with level C evidence [47]. While the initial months show heterogeneous responses, longer follow-up periods reveal more robust efficacy rates, including complete remission in specific cases [18,20,22,33,42]. However, since the response is not unanimous, it can be inferred that the efficacy of neuromodulation is determined both by intrinsic patient characteristics and by the methodological design of the studies.

In addition to the quantitative dimension, VNS demonstrates variable efficacy according to seizure semiology, with particularly expressive benefits in atonic seizures [18,22,23,28–30,42], as well as consistent results in tonic seizures [18,24,28,30,34,42,44] and absence seizures [24,28–30,42,44]. The impact of the intervention transcends numerical control, being reflected in

reduced severity and duration of events, as well as improvement in elementary secondary outcomes, such as alertness, attention, and sleep quality.

4.1 REGARDING EFFICACY: AN ASSESSMENT OF SEIZURE NUMBER AND QUALITY

The analysis of the articles included in this review showed that the overall response in reducing epileptic seizures in patients with LGS was positive. Of the total sample of 456 patients, 30 presented an increase in the number of seizures, 46 showed an indifferent response, and 375 indicated clinical improvement of at least 50% in episode reduction. Among these responders, 28 children became free of all types of seizures. Additionally, two deaths and three device removals were recorded, which will be detailed subsequently.

From the individual perspective of the reviewed articles, the study with the largest sample (Orosz et al. [39]) indicated that the impact of the intervention varies according to the predominant type of epileptic seizure in the patient. In this study, although the reduction in seizure frequency was not highly expressive, most of the sample presented generalized tonic-clonic seizures. This finding supports the premise that the best responders in LGS are patients whose predominant symptoms involve drop attacks [28,29].

In the study by Frost et al. [29], atonic seizures (drop attacks) showed an expressive reduction after Vagus Nerve Stimulation (VNS), a result similar to that described in other studies in the literature [9,48]. This finding highlights the relevance of the intervention, given that children with this condition experience seizures severe enough to require helmets to prevent head trauma [49].

The set of studies showed that the patients who benefited most from the intervention were those experiencing atonic, tonic, and absence seizures; the latter two were evidenced in the studies by Flesler et al. [28], Frost et al. [29], Cukiert et al. [24], Kruse et al. [34], Halbook et al. [30], Rossignol et al. [42], and Tekin et al. [44].

It should be emphasized that, in the complete sample of this review (n=456), not all patients presented the same initial clinical condition. The medications used for LGS control differed, as did associated comorbidities, age, and previous surgeries. In the study by Cukiert et al. [24], patients previously submitted to callosotomy or cortical resection responded satisfactorily to VNS, demonstrating that neuromodulatory techniques may be applied in individuals submitted to conventional surgical procedures. These findings are reinforced by Katagiri et al. [33].

This initial clinical asymmetry may explain the heterogeneity of responses to VNS. Furthermore, such variation is associated with the fact that the studies used different electrodes, as well as different stimulation patterns.

In this regard, the American Academy of Neurology (AAN) recommends that initial stimulation parameters follow the protocols of its guideline [49]. These parameters establish: output current of 0.25 mA, signal frequency of 30 Hz, pulse width of 250–500 μ s, “on” time of 30 seconds, and “off” time of 300 seconds (5 minutes), with the current usually increased to 2–3 mA according to tolerance. It is observed that some bibliographic references used in the preparation of that guideline coincide with the studies reviewed herein.

4.2 REGARDING SECONDARY OUTCOMES

As previously described, secondary outcomes were subjectively assessed and are therefore biased.

The attention and alertness parameter emerged as one of the most relevant secondary outcomes. This relevance stems from the fact that individuals with LGS have impaired attention and alertness because they experience persistent interictal epileptiform discharges that disrupt cognitive networks [50], disorganization of functional brain networks [51], and episodes of non-convulsive status epilepticus [6].

Another secondary outcome variable was improvement in verbal and social communication. This is affected in patients with LGS due to mechanisms of progressive cognitive deterioration affecting 75 to 95% of patients, persistent epileptiform activity interfering with cortical networks responsible for language and social processing, underlying structural brain lesions, and cognitive adverse effects of antiepileptic medications [2,6,52,53].

The concept of honeymoon also appeared as a consequence of VNS in two analyzed studies. This HM period is characterized by temporary seizure relief with improvement in quality of life and cognitive function, but may create expectations that may not be sustained in the long term [6].

Moreover, medication reduction may also be one of the secondary outcomes of interest to patients. Among the reviewed articles, only Preto Mimura et al. [41] evaluated this point, which unfortunately confirms that not all studies were concerned with verifying all variables accompanying the postoperative period of VNS in patients with LGS.

4.3 REGARDING ADVERSE EFFECTS OF VAGUS NERVE STIMULATION

The adverse effects of Vagus Nerve Stimulation (VNS) were evaluated asymmetrically across the reviewed studies. The most frequently reported events included postoperative infection, pain at the surgical site, respiratory problems, and dysphagia. The first two were expected, since they

constitute risks inherent to any surgical procedure. In the study by Parker et al. [40], removal of one of the devices due to infectious complications was reported.

Dysphagia and respiratory disorders after VNS implantation result from two pathophysiological mechanisms: direct surgical injury to the vagus nerve and electrical stimulation of the laryngeal efferent fibers. Both mechanisms converge toward vocal fold dysfunction and airway impairment [48,54]. Based on the same anatomical rationale, voice alteration and hoarseness also present as expected adverse effects.

The study by Rossignol et al. [42] indicated two relevant points regarding adverse effects: the first refers to patient number 8, whose severe dysphagia culminated in device removal; the second concerns patient number 6, who died due to airway obstruction during feeding, a fatality that was not clearly attributed to VNS. In addition to this report, one death was reported by Bremer et al. [22], involving a child who suffered sudden death of unknown etiology, with the event considered a consequence of epilepsy rather than a side effect of stimulation.

Finally, the article by Buoni et al. [23] was the only one to report intractable headache after VNS, observed in patient number 2. The condition worsened with the increase in electrical current to 1.25 mA, followed by increased seizure frequency and intensity. The current was reduced ten days after symptom onset and, subsequently, the generator was removed at the patient's request due to ineffectiveness. The mechanism of this intense headache probably results from activation of the trigeminovagal system—an area of extensive anatomical connections in the brainstem—generating nociceptive activation of the nerve at rest [55].

4.4 LIMITATIONS

The main limitation of this study lies in the use of retrospective cohort studies. Such studies are considered lower-quality evidence compared with randomized clinical trials (RCTs), primarily due to the absence of randomization, which makes them vulnerable to systematic biases that may distort estimates of an intervention effect. This methodological weakness was reflected in the fact that all analyzed articles presented serious or critical risk of bias.

Furthermore, sample sizes were mostly small. Although LGS is a rare syndrome—which justifies a generally smaller number of participants (n)—the bibliographies used lack samples with statistical significance specific to the syndrome. This scarcity reinforces the understanding that conducting RCTs on this topic is more complex. Still regarding sampling, deaths and loss to follow-up represented points of attention, as they made the sample variable over time.

The absence of standardization among articles regarding follow-up duration, electrode stimulation parameters, previous clinical conditions, age, and outcome definitions also represented

an important limitation, since the search for uniform results originated from distinct clinical scenarios.

In addition to the above, a central limitation of this review refers to the high risk of bias in Domain 5 of the ROBINS-I tool (bias in outcome measurement), classified as serious or critical in 100% of the included studies. The consistency of this finding suggests the presence of structural limitations inherent to studies assessing VNS in the context of LGS, beyond isolated methodological flaws. Among the main determinants of this bias, the practical impossibility of blinding stands out. As this is a surgical intervention with device implantation, frequently associated with perceptible physical signs, most studies adopt an open-label design. This characteristic exposes outcome assessment to measurement bias, since participants, caregivers, and assessors are aware of the intervention performed.

Additionally, the primary outcomes are predominantly subjective, based on seizure frequency reported by caregivers. The use of seizure diaries introduces variability in data quality, being subject to perception, memory, and expectation biases. This aspect is particularly relevant in contexts of pediatric refractory epilepsy, in which the clinical and emotional impact of the intervention may influence outcome recording.

The distinction between serious and critical risk-of-bias classifications in this domain was mainly associated with methodological rigor in measurement. Studies classified as “serious” tended to use prospective records and standardization strategies, whereas those with “critical” risk presented additional limitations, such as retrospective collection based on memory or insufficient description of measurement methods. Finally, the absence of control groups with sham procedures limits the distinction between the physiological effects of stimulation and improvements resulting from therapeutic expectations, a phenomenon described as the surgical placebo effect.

Thus, the uniform classification in Domain 5 reflects limitations intrinsic to the available literature and should be considered when interpreting the findings and planning future research.

The primary expectation established from this review is that it will impact the execution of research on LGS and VNS. It is suggested to adopt defined standards for outcomes, initial clinical presentations, and at least initial electrical stimulation parameters. It is also recommended to use a population exclusively with LGS in the sample, given that during the preparation of this study, the population was screened to exclude data "contamination" from other childhood epileptic syndromes, such as Dravet Syndrome.

Finally, as a secondary expectation, it is projected that studies focusing exclusively on LGS and VNS will be able to define, with greater diagnostic certainty, the impact of the intervention on the quality of life of patients affected by this pathology.

CONCLUSION

This systematic review suggests that Vagus Nerve Stimulation (VNS) may represent a potentially useful therapeutic alternative in the management of refractory Lennox-Gastaut Syndrome (LGS). The included studies indicate clinical benefit in a considerable proportion of the pediatric patients evaluated, especially in the reduction of atonic, tonic, and absence seizures. However, the available evidence presents relevant methodological limitations, with predominance of retrospective and observational studies, as well as high risk of bias, which limits definitive conclusions regarding the efficacy and safety of the intervention.

In addition to the reduction in epileptic seizure frequency, the studies reported possible improvements in qualitative outcomes, particularly alertness, attention, and sleep quality. These findings have clinical relevance, considering that cognitive impairment associated with LGS may be aggravated by persistent interictal discharges, potentially modulated by vagal neuromodulation. Regarding safety, the most frequently described adverse effects were dysphagia and voice changes, generally attributed to the expected pathophysiological mechanisms of stimulation and, in most cases, without the need for treatment discontinuation.

The methodological quality assessment using the ROBINS-I tool identified a high risk of bias, particularly in the outcome measurement domain, due to the lack of blinding and the reliance on subjective caregiver reports. Heterogeneity among the studies was also observed regarding stimulation parameters, follow-up duration, and the patients' clinical characteristics. Therefore, it is emphasized that future studies should be prospective cohorts exclusive to patients with LGS, featuring representative samples and standardized VNS protocols, in order to generate methodologically more robust evidence. Until new studies in this format become available, this systematic review can guide individualized and assertive approaches in the management of LGS.

References

- [1] Camfield P, Camfield C. Epileptic syndromes in childhood: clinical features, outcomes, and treatment. *Epilepsia* 2002;43 Suppl 3:27–32. <https://doi.org/10.1046/j.1528-1157.43.s.3.3.x>.
- [2] Asadi-Pooya A. Lennox-Gastaut syndrome: a comprehensive review. *NEUROLOGICAL SCIENCES* 2018;39:403–14. <https://doi.org/10.1007/s10072-017-3188-y>.
- [3] Vignoli A, Oggioni G, De Maria G, Peron A, Savini MN, Zambrelli E, et al. Lennox–Gastaut syndrome in adulthood: Long-term clinical follow-up of 38 patients and analysis of their recorded seizures. *Epilepsy Behav* 2017;77:73–8. <https://doi.org/10.1016/j.yebeh.2017.09.006>.
- [4] Kossoff EHW, Shields WD. Nonpharmacologic care for patients with Lennox-Gastaut syndrome: Ketogenic diets and vagus nerve stimulation. *Epilepsia* 2014;55:29–33. <https://doi.org/10.1111/epi.12546>.
- [5] Vasquez A, Fine AL. Dietary therapies in Lennox-Gastaut syndrome. *Seminars in Pediatric Neurology* 2025;56:101238. <https://doi.org/10.1016/j.spen.2025.101238>.
- [6] Arzimanoglou A, French J, Blume W, Cross J, Ernst J, Feucht M, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. *LANCET NEUROLOGY* 2009;8:82–93. [https://doi.org/10.1016/S1474-4422\(08\)70292-8](https://doi.org/10.1016/S1474-4422(08)70292-8).
- [7] Shields LBE, Oluigbo CO, Karakas C. Neuromodulation in Lennox-Gastaut Syndrome: Emerging therapies and future directions. *Seminars in Pediatric Neurology* 2025;56:101237. <https://doi.org/10.1016/j.spen.2025.101237>.
- [8] Gélisse P, Crespel A, Genton P, Dravet C. History of Lennox-Gastaut Syndrome: Sixty Years of Advancements in Therapeutic Practices. *Seizure: European Journal of Epilepsy* 2026;134:165–72. <https://doi.org/10.1016/j.seizure.2025.12.004>.
- [9] Samanta D, Naik S. Seizure-type-specific treatment responses in Lennox-Gastaut Syndrome: A comprehensive review of pharmacological, neuromodulatory, dietary, and surgical therapies. *Epilepsy Behav* 2025;170:110472. <https://doi.org/10.1016/j.yebeh.2025.110472>.
- [10] Samanta D. Management of Lennox-Gastaut syndrome beyond childhood: A comprehensive review. *Epilepsy Behav* 2021;114. <https://doi.org/10.1016/j.yebeh.2020.107612>.
- [11] Thirunavu V, Du R, Wu JY, Berg AT, Lam SK. The role of surgery in the management of Lennox–Gastaut syndrome: A systematic review and meta-analysis of the clinical evidence. *Epilepsia* 2021;62:888–907. <https://doi.org/10.1111/epi.16851>.
- [12] Sharawat I, Panda P, Sihag R, Panda P, Dawman L. Efficacy and safety of corpus callosotomy and ketogenic diet in children with Lennox Gastaut syndrome: a systematic review and meta-analysis. *CHILDS NERVOUS SYSTEM* 2021;37:2557–66. <https://doi.org/10.1007/s00381-021-05174-z>.
- [13] Soares D, de Aguiar P. Callosotomy vs Vagus Nerve Stimulation in the Treatment of Lennox-Gastaut Syndrome: A Systematic Review With Meta-Analysis. *NEUROMODULATION* 2023;26:518–28. <https://doi.org/10.1016/j.neurom.2022.06.005>.
- [14] You S, Kang H, Ko T, Kim H, Yum M, Hwang Y, et al. Comparison of corpus callosotomy and vagus nerve stimulation in children with Lennox-Gastaut syndrome. *BRAIN & DEVELOPMENT* 2008;30:195–9. <https://doi.org/10.1016/j.braindev.2007.07.013>.
- [15] Armeno ML, Kossoff EH. Let food be thy medicine. The interaction between ketogenic diet therapy and anti-seizure medications: A systematic review. *Epileptic Disorders* 2023;25:18–27. <https://doi.org/10.1002/epd2.20055>.
- [16] Lyons P, Wheless J, Verner R, Ferreira J, Liow K, Valeriano J, et al. Vagus nerve stimulation in Lennox–Gastaut syndrome: Twenty-four-month data and experience from the CORE-VNS study. *Epilepsia* 2025;66:1540–9. <https://doi.org/10.1111/epi.18289>.
- [17] Hajnsek S, Petelin Z, Poljaković Z, Mrak G, Paladino J, Desnica A. Vagus nerve stimulation in the treatment of patients with pharmacoresistant epilepsy: our experiences. *Coll Antropol* 2011;35:755–60.
- [18] Shahwan A, Bailey C, Maxiner W, Harvey A. Vagus nerve stimulation for refractory epilepsy in children: More to VNS than seizure frequency reduction. *EPILEPSIA* 2009;50:1220–8. <https://doi.org/10.1111/j.1528-1167.2008.01940.x>.
- [19] Dibué M, Greco T, Spoor J, Tahir Z, Specchio N, Hänggi D, et al. Vagus nerve stimulation in patients with Lennox-Gastaut syndrome: A meta-analysis. *ACTA NEUROLOGICA*

- SCANDINAVICA 2021;143:497–508. <https://doi.org/10.1111/ane.13375>.
- [20] Abdelmoity S, Abdelmoity A, Riordan S, Kaufman C, Le Pichon J, Abdelmoity A. The efficacy and tolerability of auto-stimulation-VNS in children with Lennox-Gastaut syndrome. *SEIZURE-EUROPEAN JOURNAL OF EPILEPSY* 2021;86:168–74. <https://doi.org/10.1016/j.seizure.2021.02.015>.
- [21] Alanazi GM, Alosaimi TF, Alwadei AH, Al-Otaibi AD, Jad LA, Al-Attas AA. Efficacy and safety of corpus callosotomy versus vagus nerve stimulation as long-term adjunctive therapies in children with Lennox–Gastaut syndrome Experience of a tertiary care center. *Neurosciences* 2022;27:59–64. <https://doi.org/10.17712/nsj.2022.2.20210135>.
- [22] Bremer A, Eriksson A-S, Røste GK, Knudtzen B, Nakken KO. Vagal nerve stimulation in children with difficult-to-treat epilepsy. *Tidsskr Nor Laegeforen* 2006;126:896–8.
- [23] Buoni S, Mariottini A, Pieri S, Zalañi A, Farnetani MA, Strambi M, et al. Vagus nerve stimulation for drug-resistant epilepsy in children and young adults. *Brain Dev* 2004;26:158–63. [https://doi.org/10.1016/S0387-7604\(03\)00120-7](https://doi.org/10.1016/S0387-7604(03)00120-7).
- [24] Cukiert A, Cukiert C, Burattini J, Lima A, Forster C, Baise C, et al. A Prospective Long-Term Study on the Outcome After Vagus Nerve Stimulation at Maximally Tolerated Current Intensity in a Cohort of Children With Refractory Secondary Generalized Epilepsy. *NEUROMODULATION* 2013;16:551–6. <https://doi.org/10.1111/j.1525-1403.2012.00522.x>.
- [25] Cukiert A, Cukiert C, Guimaraes RB, Burattini JA, Vieira JV, de Oliveira JPS. Vagus Nerve Stimulation Electrode Impedance Over Time in Children With Lennox-Gastaut Syndrome. *Neuromodulation* 2024;27:789–91. <https://doi.org/10.1016/j.neurom.2023.06.006>.
- [26] Elliott R, Rodgers S, Bassani L, Morsi A, Geller E, Carlson C, et al. Vagus nerve stimulation for children with treatment-resistant epilepsy: a consecutive series of 141 cases Clinical article. *JOURNAL OF NEUROSURGERY-PEDIATRICS* 2011;7:491–500. <https://doi.org/10.3171/2011.2.PEDS10505>.
- [27] Fang T, Xie Z-H, Liu T-H, Deng J, Chen S, Chen F, et al. Preliminary analysis of the effect of vagus nerve stimulation in the treatment of children with intractable epilepsy. *World J Clin Cases* 2020;8:5918–25. <https://doi.org/10.12998/wjcc.v8.i23.5918>.
- [28] Flesler S, Reyes G, Fortini S, Ramos B, Cersósimo R, Bartuluchi M, et al. Vagus nerve stimulation: treatment of 158 pediatric patients with a long-term follow-up. *REVISTA DE NEUROLOGIA* 2017;64:496–501. <https://doi.org/10.33588/rn.6411.2016458>.
- [29] Frost M, Gates J, Helmers S, Wheless J, Levisohn P, Tardo C, et al. Vagus nerve stimulation in children with refractory seizures associated with Lennox-Gastaut syndrome. *EPILEPSIA* 2001;42:1148–52. <https://doi.org/10.1046/j.1528-1157.2001.23900.x>.
- [30] Hallböök T, Lundgren J, Stjernqvist K, Blennow G, Strömlad L, Rosén M. Vagus nerve stimulation in 15 children with therapy resistant epilepsy; its impact on cognition, quality of life, behaviour and mood. *SEIZURE-EUROPEAN JOURNAL OF EPILEPSY* 2005;14:504–13. <https://doi.org/10.1016/j.seizure.2005.08.007>.
- [31] Hentati E, Ben Ali N, Kchaou M, Belal S. Surgical palliative care in Lennox-Gastaut syndrome. *J Neurol Sci* 2013;333:e50. <https://doi.org/10.1016/j.jns.2013.07.178>.
- [32] Hosain S, Nikalov B, Harden C, Li M, Fraser R, Labar D. Vagus nerve stimulation treatment for Lennox-Gastaut syndrome. *J Child Neurol* 2000;15:509–12. <https://doi.org/10.1177/088307380001500803>.
- [33] Katagiri M, Iida K, Kagawa K, Hashizume A, Ishikawa N, Hanaya R, et al. Combined surgical intervention with vagus nerve stimulation following corpus callosotomy in patients with Lennox-Gastaut syndrome. *Acta Neurochir* 2016;158:1005–12. <https://doi.org/10.1007/s00701-016-2765-9>.
- [34] Kruse B, Bauer A, Johannsen J, Wenner K, Wessig K. Vagus nerve stimulation in epileptic encephalopathies. *Z Epileptologie* 2010;23:189–93. <https://doi.org/10.1007/s10309-010-0118-x>.
- [35] Lagae L, Verstegen A, Jansen K. Vagus nerve stimulation in children with refractory epilepsy: Age at implantation as a predictor of better efficacy. *Paediatr Croat* 2012;56:105–9.
- [36] Lundgren J, Amark P, Blennow G, Strömlad LG, Wallstedt L. Vagus nerve stimulation in 16 children with refractory epilepsy. *Epilepsia* 1998;39:809–13. <https://doi.org/10.1111/j.1528-1157.1998.tb01173.x>.
- [37] Majoie HJM, Berfelo MW, Aldenkamp AP, Renier WO, Kessels AGH. Vagus nerve stimulation

- in patients with catastrophic childhood epilepsy, a 2-year follow-up study. *Seizure* 2005;14:10–8. <https://doi.org/10.1016/j.seizure.2004.02.003>.
- [38] Mikati MA, Ataya NF, El-Ferezli JC, Baghdadi TS, Turkmani AH, Comair YG, et al. Quality of life after vagal nerve stimulator insertion. *Epileptic Disord* 2009;11:67–74. <https://doi.org/10.1684/epd.2009.0244>.
- [39] Orosz I, McCormick D, Zamponi N, Varadkar S, Feucht M, Parain D, et al. Vagus nerve stimulation for drug-resistant epilepsy: A European long-term study up to 24 months in 347 children. *Epilepsia* 2014;55:1576–84. <https://doi.org/10.1111/epi.12762>.
- [40] Parker APJ, Polkey CE, Binnie CD, Madigan C, Ferrie CD, Robinson RO. Vagal nerve stimulation in epileptic encephalopathies. *Pediatrics* 1999;103:778–82. <https://doi.org/10.1542/peds.103.4.778>.
- [41] Preto Mimura PM, Farias IB, Seguti Ferreira L, Barbosa AL. Follow-up of neuropsychiatric patients treated with vagus nerve stimulation. *J Neurol Sci* 2017;381:683. <https://doi.org/10.1016/j.jns.2017.08.1922>.
- [42] Rossignol E, Lortie A, Thomas T, Bouthiller A, Scavarda D, Mercier C, et al. Vagus nerve stimulation in pediatric epileptic syndromes. *Seizure* 2009;18:34–7. <https://doi.org/10.1016/j.seizure.2008.06.010>.
- [43] Rychlicki F, Zamponi N, Trignani R, Ricciuti RA, Iacoangeli M, Scerrati M. Vagus nerve stimulation: clinical experience in drug-resistant pediatric epileptic patients. *Seizure* 2006;15:483–90. <https://doi.org/10.1016/j.seizure.2006.06.001>.
- [44] Tekin H, Köse S, Gökben S, Erermis S, Turhan T, Tekgül H, et al. The Effect of Vagal Nerve Stimulation on the Quality of Life in Pediatric Cases. *JOURNAL OF PEDIATRIC RESEARCH* 2017;4:137–42. <https://doi.org/10.4274/jpr.43434>.
- [45] Tormasiova M, Kollova A, Bratsky L. Immediate postimplantation effect of baseline stimulation parameters of vagus nerve stimulation in patients with refractory epilepsy. *Stereotactic Funct Neurosurg* 2014;92:s216. <https://doi.org/10.1159/000367644>.
- [46] Zamponi N, Passamonti C, Cesaroni E, Trignani R, Rychlicki F. Effectiveness of vagal nerve stimulation (VNS) in patients with drop-attacks and different epileptic syndromes. *Seizure* 2011;20:468–74. <https://doi.org/10.1016/j.seizure.2011.02.011>.
- [47] Morris GL, Gloss D, Buchhalter J, Mack KJ, Nickels K, Harden C. Evidence-based guideline update: Vagus nerve stimulation for the treatment of epilepsy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2013;81:1453–9. <https://doi.org/10.1212/WNL.0b013e3182a393d1>.
- [48] Ryvlin P, Rheims S, Hirsch LJ, Sokolov A, Jehi L. Neuromodulation in epilepsy: state-of-the-art approved therapies. *The Lancet Neurology* 2021;20:1038–47. [https://doi.org/10.1016/S1474-4422\(21\)00300-8](https://doi.org/10.1016/S1474-4422(21)00300-8).
- [49] Guerrini R. Epilepsy in children. *The Lancet* 2006;367:499–524. [https://doi.org/10.1016/S0140-6736\(06\)68182-8](https://doi.org/10.1016/S0140-6736(06)68182-8).
- [50] Warren AEL, Harvey AS, Vogrin SJ, Bailey C, Davidson A, Jackson GD, et al. The epileptic network of Lennox-Gastaut syndrome: Cortically driven and reproducible across age. *Neurology* 2019;93:e215–26. <https://doi.org/10.1212/WNL.0000000000007775>.
- [51] Brigo F, Jones K, Eltze C, Matricardi S. Anti-seizure medications for Lennox-Gastaut syndrome. *Cochrane Database Syst Rev* 2021;4:CD003277. <https://doi.org/10.1002/14651858.CD003277.pub4>.
- [52] Elger CE, Helmstaedter C, Kurthen M. Chronic epilepsy and cognition. *The Lancet Neurology* 2004;3:663–72. [https://doi.org/10.1016/S1474-4422\(04\)00906-8](https://doi.org/10.1016/S1474-4422(04)00906-8).
- [53] Pino AF, Naik S, Erdemir G. Lennox-Gastaut syndrome: Comorbidities and clinical implications. *Seminars in Pediatric Neurology* 2025;56:101239. <https://doi.org/10.1016/j.spen.2025.101239>.
- [54] Giordano F, Zicca A, Barba C, Guerrini R, Genitori L. Vagus nerve stimulation: Surgical technique of implantation and revision and related morbidity. *Epilepsia* 2017;58:85–90. <https://doi.org/10.1111/epi.13678>.
- [55] Lyubashina OA, Sokolov AY, Panteleev SS. Vagal afferent modulation of spinal trigeminal neuronal responses to dural electrical stimulation in rats. *Neuroscience* 2012;222:29–37. <https://doi.org/10.1016/j.neuroscience.2012.07.011>.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

Funding

No funding was received for the conduct of this study, and none of the authors received financial support for the preparation of this manuscript.