Seizure 50 (2017) 147–152

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Meta-Analysis

# Efficacy of adjunctive vagus nerve stimulation in patients with Dravet syndrome: A meta-analysis of 68 patients

Maxine Dibué-Adjei[a,*], Igor Fischer[b], Hans-Jakob Steiger[b], Marcel Alexander Kamp[b]

[a] LivaNova Deutschland GmbH, LivaNova PLC-owned subsidary, Lindberghstr 25, 80939 Munich, Germany
[b] Department of Neurosurgery, Medical Faculty, Heinrich-Heine-University, Moorenstraße 5, D-40225 Düsseldorf, Germany

ARTICLE INFO

*Article history:*
Received 19 May 2017
Received in revised form 5 June 2017
Accepted 11 June 2017

*Keywords:*
Dravet syndrome
SCN1A
Rare disease
Vagus nerve stimulation
VNS
Neuromodulation
Refractory epilepsy

ABSTRACT

*Rationale:* Dravet Syndrome (DS) is a severe epileptic encephalopathy of childhood involving intractable seizures, recurrent status epilepticus and cognitive decline. Because DS is a rare disease, available data is limited and evidence-based treatment guidelines are lacking. Vagus nerve stimulation (VNS) is an established neurostimulation treatment for intractable epilepsy, however little evidence is published on its efficacy in patients with DS.
*Methods:* We performed a meta-analysis of all peer-reviewed English language studies reporting seizure outcomes of patients with DS treated with adjunctive vagus nerve stimulation. The primary and secondary outcome measures were ≥50% reduction of seizures or of the most-debilitating seizure type and seizure reduction per patient.
*Results:* 13 studies comprising 68 patients met the inclusion criteria of which 11 were single-center retrospective case series, one was a multi-center retrospective analysis and one was a case report. 52.9% of patients experienced a ≥50% reduction of seizures and the average seizure reduction, which could only be assessed in n = 28 patients was 50.8%. 7 out of 13 studies reported additional benefits of VNS, however this could not be assessed systematically.
*Conclusion:* Vagus nerve stimulation appears to reduce seizure frequency in patients with DS. Based on this preliminary analysis, controlled trials of VNS in this rare condition using patient-centric outcome measures are indicated.
© 2017 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.

## 1. Introduction

Severe myoclonic epilepsy of infancy (SMEI) was first decribed by Charlotte Dravet in 1978 and later renamed to "Dravet Syndrome" to include atypical and borderline forms as well as to describe the syndrome that persists beyond infancy [11,12]. Dravet syndrome (DS) is an infantile-onset epileptic encephalopathy of childhood involving intractable seizures, recurrent status epilepticus and cognitive decline [13,14]. The majority of patients with DS carry a loss-of-function mutation of the SCN1A gene that codes for the alpha1 subunit of the voltage-gated sodium channel $Na_v1.1$ [23], which is expressed in both excitatory and inhibitory neurons [40]. Initial presentation of DS is quite characteristic: within the first year of life a developmentally normal child presents with prolonged clonic, generalized, or unilateral seizures triggered by fever or hyperthermia, often after vaccination or a warm bath [12,28,31]. Patients then develop multiple seizure types with both non-convulsive and convulsive seizures evolving into status epilepticus and by age-2 intellectual disability and neurological deficits are typically evident [5,12]. Patients with DS are at a high risk for premature death (16–17 per 1000 patient years), with sudden-unexpected-death in epilepsy (SUDEP) remarkably representing the leading cause of death in childhood followed by status epilepticus [9,37]. Because Dravet Syndrome is rare, occurring approximately once per 16 000 births [42], available data is limited and evidence-based treatment guidelines are lacking. Treatment of DS remains challenging and as seizure-freedom is rarely achieved [8] recently published recommendations by a North American Consensus Panel employing the Delphi approach, strongly endorse that the highest priority should be avoiding prolonged convulsive seizures and obtundation status given their morbidity and impact on developmental outcome [41].

Vagus Nerve Stimulation (VNS) was approved for adjunctive therapy of drug resistant epilepsy (DRE) in Europe in 1994 and in the USA in 1997 and involves intermittent electrical stimulation of the left cervical vagus nerve by an implanted helical electrode that

* Corresponding author.
*E-mail address:* maxine.dibue-adjei@livanova.com (M. Dibué-Adjei).

http://dx.doi.org/10.1016/j.seizure.2017.06.007
1059-1311/© 2017 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.

is connected to a pulse generator. Long-term studies in heterogeneous DRE populations show that VNS elicits a > 50% reduction in seizure frequency in approximately 60% of patients [16,17]; reduces the incidence of convulsive status epilepticus and reduces seizure severity in approximately 40% of patients [24]. Complete seizure control is rare with VNS: only approximately 20% of patients achieve >90% seizure reduction and approximately 8% achieve seizure freedom [16,17].

The North American Consensus Panel only reports moderate consensus for the use of VNS in DS, recommending VNS after failure of first and second line treatments consisting of (1) valproic acid and clobazam and (2) add-on stiripentol or topiramate or the ketogenic diet. No consensus was reached on whether on-demand VNS (eliciting an additional stimulation aimed at interrupting an occurring seizure by swiping a 50 G magnet over the implanted VNS generator) is effective in interrupting prolonged seizures. The

**Table 1**
Characteristics of the 13 included studies.

| Reference | Total # of patients | # of patients with DS receiving VNS | Study design | AAN Class | # of DS patients with ≥50% SR (%) | Length of Follow-up | Adverse Events | Further Patient Outcome | Study Limitations |
|---|---|---|---|---|---|---|---|---|---|
| Orosz et al. (2014) | 347 | 13 | retrospective multi-center | III | 5 (38%) | 24 months | not reported specifically for DS | not reported specifically for DS | -retrospective<br>-only predominant seizure type assessed |
| Fulton et al. (2017) | 12 | 12 | retrospective single-center | III | 9 (75%) | ≥6 months | not reported | -cognitive and speech improvements in 4 out of 9 responders | -retrospective<br>-only GTCS assessed |
| Dressler et al. (2015) | 32 | 8 | retrospective single-center | III | 3 (38%) | 3 months | not reported | not reported | -retrospective<br>-short FU outside of therapeutic window of VNS |
| Sirsi et al. (2016) | 8 | 8 | retrospective single-center | III | 4 (50%) | ≥12 months: | stimulation intensity had to be decreased in 2 patients due to coughing and hoarseness | -cessation of SE in one non-responder<br>-caregivers of 2patients reported subjective improvement in alertness and interaction | retrospective |
| Zamponi et al. (2011) | 8 | 8 | retrospective single-center | III | 4 (50%) | 12 months | no intra- or post-surgical complications or long-term side effects observed | -Cognitive level was unchanged in all patients.<br>-One patient showed a clinically relevant improvement in adapting behavior<br>-7 patients experienced a slight improvement in alertness and communicative skills | retrospective |
| Dlouhy et al. (2016) | 6 | 6 | retrospective single-center | III | 4 (67%) | ≥12 months | not reported | not reported | -retrospective<br>-one patient underwent callosotomy after VNS |
| Caraballo et al. (2011) | 59 | 3 | retrospective single-center | III | 2 (66%) | ≥24 months | -Transient pain at implantation site & hoarseness (n = 2) disappeared after stimulation adjustments.<br>-One patient had an infection that was not resolved | -EEG abnormalities improved in the two responders one year after implantation | -retrospective |
| Cersósimo et al. (2011) | 64 | 3 | retrospective single-center | III | 1 (33%) | ≥23 months | not reported specifically for DS | one non-responder reported decreased post-ictal severity | retrospective |
| Shahwan et al. (2009) | 26 | 2 | retrospective single-center | III | 1 (50%) | ≥18 months | none | -cessation of status epilepticus<br>-SUDEP occurred in responder after 6 years | retrospective |
| Rossignol et al. (2009) | 28 | 2 | retrospective single-center | III | 1 (50%) | 24 months | not reported specifically for DS | not reported specifically for DS | retrospective |
| Chen et al. (2012) | 8 | 1 | retrospective single-center | III | 1 (100%) | 24 months | hoarseness | not reported specifically for DS | retrospective |
| Kang et al. (2006) | 16 | 1 | retrospective single-center | III | 0 (0%) | ≥12 months | hoarseness | not reported | retrospective |
| Spatola et al. (2013) | 1 | 1 | case-report | IV | 1 (100%) | 28 months | not reported | -alertness and cognition improved<br>-magnet use shortens seizures<br>-reduced AED burden | reporting bias |

panel concludes that VNS has a minimal to moderate impact on seizure reduction but is generally less efficacious than the ketogenic diet [41].

Evidence for efficacy of VNS in DS is very scarce and restricted to case reports, small case series and subgroups of DS patients in VNS trials. The largest case-series of intractable epilepsy associated With SCN1A gene abnormalities treated with VNS was published recently and reported >50% reduction in generalized tonic-clonic seizures (GTCS) in 9 out of 12 patients who were implanted in-house and "marked improvement" or seizure freedom in 4 out of 8 patients who were implanted at other institutions [19]. Of the 12 patients implanted in-house 7 had a >75% reduction of GTCSs raising the question whether VNS may be effective in reducing GTCS, often the most debilitating seizure type in this patient group. Contrastingly, a European multicenter trial on VNS in children with drug-resistant epilepsy which included a subgroup of patients with DS found that patients with DS and patients with predominantly GTCS showed an improvement that was marginally lower compared to the entire population for which a responder rate of 44% was calculated at 24 months [29].

A new and emerging approach to overcoming the lack of clinical data associated with orphan diseases is the use of social media. A recent investigation employing an online questionnaire obtained responses from 49 care-givers of children with DS receiving VNS. Only 28.5% of care-givers reported a >50% decrease in seizure frequency after VNS placement, however interestingly 84% reported improved seizure severity, 48% reported a reduction in hospital visits and there was a statistically significant reduction in the amount of antiepileptic drugs used [2].

Because single epilepsy centers typically do not have enough patients with DS to systematically assess efficacy of VNS for this severe orphan disease we have performed a meta-analysis of reported cases in the literature to gain greater insight into the extent of VNS efficacy for patients with DS.

## 2. Methods

### 2.1. Compliance with ethical standards

This article does not contain any studies with human participants or animals performed by any of the authors.

### 2.2. Study design

The present meta-analysis was modeled after the preferred reporting items for systematic reviews and meta-analyses (PRISMA) and adheres to a structured review protocol [27].

### 2.3. Selection criteria

We systematically searched the PubMed database for publications reporting the effect of VNS on seizure frequency in patients with "Dravet Syndrome", "Severe Myoclonic Epilepsy of Infancy" or "Severe Myoclonic Epilepsy of Infancy Borderline". Because preliminary PubMed searches revealed very small numbers of eligible publications a broader search approach was employed by searching for the terms "Dravet Syndrome", "Severe Myoclonic Epilepsy of Infancy", "SMEI", "SMEIB" in combination with the terms "Vagus Nerve Stimulation", "Vagal Nerve Stimulation" or "VNS". Only peer-reviewed original research published in English language were included. The primary outcome measure was ≥50% reduction of seizure frequency or of frequency of the most-debilitating seizure type at the longest follow-up reported compared to baseline. The secondary outcome measure was seizure reduction per patient at the longest follow-up reported. As the effect of VNS is time dependent, studies had to report the length of follow-up and how outcomes were assessed.

### 2.4. Article selection

Authors M.D.A. and M.A.K. independently conducted PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) searches as well as google searches using the key words listed above. The authors then independently excluded non-relevant articles based on review of the full-text articles before comparing selected articles. Eligibility criteria were then applied to the selected articles to obtain the final selection.

### 2.5. Data extraction

From each article the fraction of patients with DS experiencing a ≥50% reduction of seizure frequency or of frequency of the most-debilitating seizure type at the longest follow-up post VNS implantation was extracted. If articles reported adverse events or other effects of VNS therapy in patients with DS this information was extracted and reported in Table 1. If the relative seizure reduction from baseline was reported for individual DS patients, this data was extracted and reported in Fig. 3 Fig. 3

### 2.6. Classification of articles

Grading of level of evidence was carried out using the American Academy of Neurology's (AAN) classification scheme [20]. The AAN defines a Class I study as a randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population in which relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences. Also required are a) concealed allocation b) clearly defined primary outcome(s) c) clearly defined exclusion/inclusion criteria d) adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias e) for non-inferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required 1. the standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective) 2. the inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are substantially equivalent to those of previous studies establishing efficacy of the standard treatment 3. the interpretation of the results of the study is based on an observed-cases analysis.

A Class II study is a randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a–e Class I, above, or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e Class I, above. Relevant baseline characteristics must be presented and substantially equivalent among treatment groups or there must be appropriate statistical adjustment for differences.

Class III trials are all other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurements.

Class IV studies are those not meeting Class I, II, or III criteria including consensus or expert opinion.

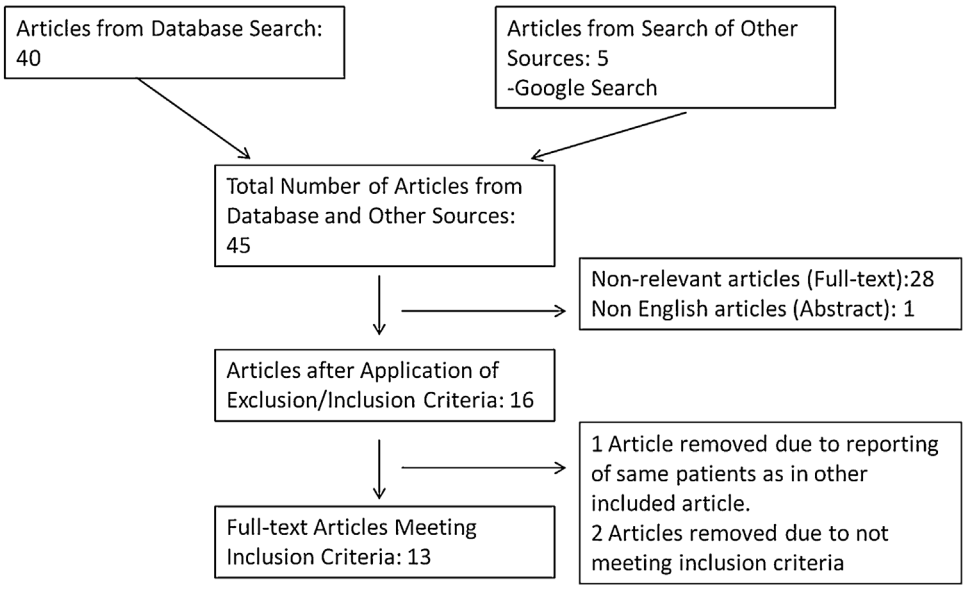


**Fig. 1.** Flow diagram of the article search.

### 2.7. Statistical analysis

Descriptive statistics (min., max., mean and median) of the fraction of patients experiencing ≥50% reduction was computed for all 13 studies. For the seven studies which reported individual reduction rates, descriptive statistics was performed once for all data and once on a per-study basis. The analysis was done using R version 3.3.2 (R Core Team).

## 3. Results

### 3.1. Study selection

Both authors (M.D.A and M.A.K.) identified 45 articles in their primary searches using the key-words mentioned in the methods section. Identification of relevant articles in English revealed one selection discrepancy between the two authors: one recently published case report by Hanaya et al. describing efficacy of VNS in a patient with a confirmed SCN1A mutation and genetic epilepsy with febrile seizures plus (GEFS+) [21]. GEFS+ refers to a familial epilepsy syndrome comprising a spectrum of phenotypes from febrile seizures to DS in which SCN1A mutations can be found in 10% of patients [34]. After further scrutiny it was decided to exclude this case report firstly as the authors clearly do not classify the patient as having a DS phenotype; secondly because there is no mention of status epilepticus and thirdly because the patients intelligence quotient was reported to be in normal range. After excluding 29 irrelevant articles application of the selection criteria led to exclusion of two articles that investigated efficacy of VNS in patients with DS (Fig. 1). One article by Fernandez et al did not report whether patients had a ≥50% reduction in seizure frequency but instead categorized seizure frequency as (1) daily multiple seizures; (2) less than daily but more than 1 seizure per week; (3) less than 1 seizure per week but more than 1 seizure per month; and (4) less than 1 seizure per month [18]. Another article by Bremer et al. failed to report how seizure frequency was assessed including a complete lack of information of length of follow-up [3]. 13 studies met the inclusion criteria comprising a total of 68 patients with Dravet Syndrome treated with vagus nerve stimulation for which changes in seizure frequency were reported

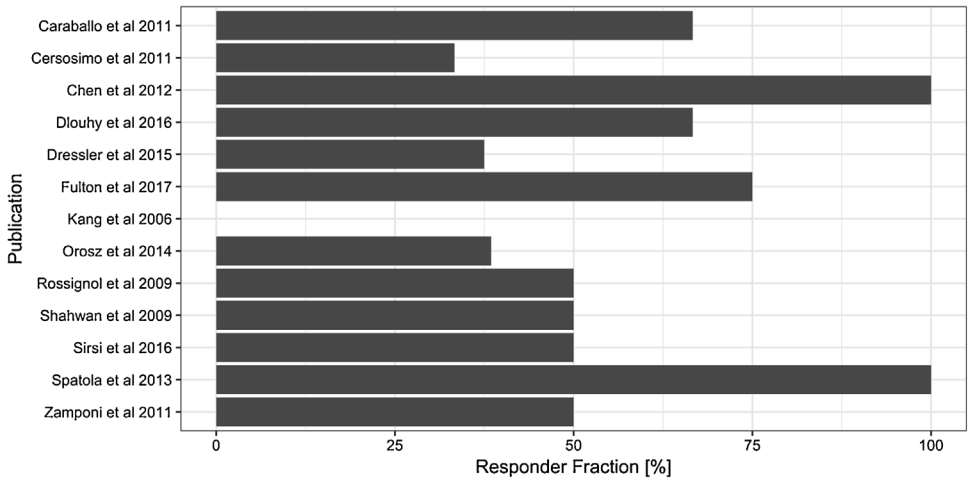


**Fig. 2.** Fraction of DS patients responding to VNS in the 13 included publications at latest follow-up reported.

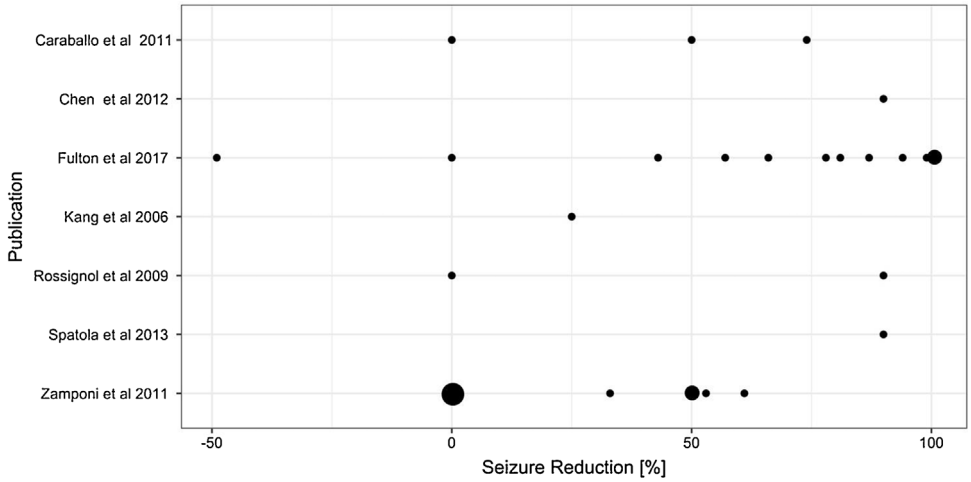


**Fig. 3.** Seizure reduction of individual DS patients at latest follow-up reported. Seizure reduction of individual patients was only reported for 28 out of the 68 patients. Mean seizure reduction was 50.8% and the median 55%. A small dot indicates one patient with this specific value of seizure reduction. Medium-sized dots indicate two patients and large dots indicate three patients within the same publication with this specific value of seizure reduction.

(Table 1) [4,6,7,10,15,19,25,29,32,35,36,38,43]. 11 out the 13 studies were single-center retrospective case series; one was a multi-center retrospective analysis and one was a case report. 9 out of 13 studies either analyzed the effect of VNS on seizure frequency in a heterogeneous patient population from which data from the DS patients was used in this analysis or also assessed another anti-epileptic therapy in patients with DS from which the data from patients treated with VNS was used in this analysis (Table 1).

### 3.2. Classification of articles

All studies were found to meet AAN Class III criteria, except the case report (Spatola et al.) which met class IV criteria [20]. Although six of the class III studies only included three or less DS patients treated with VNS, these studies can be classed higher than case reports, as they are less prone to reporting bias due to inclusion of all patients treated at that institution.

### 3.3. VNS efficacy

The reported fractions of patients experiencing ≥50% reduction varied between 0 and 100%, with a mean of 55.2% and a median of 50%. Due to different size of patient groups, the overall average responder rate was somewhat lower at 52.9%. Despite the low sample sizes of the included studies responder rates were similar in nearly all studies with more than 6 DS patients (75%, 67%, 50%, 38%, 50%, 38%) (Fig. 2).

Seizure reduction of individual patients was only reported for 28 out of the 68 patients (Fig. 3). The individual seizure reduction rates, as reported in seven studies, varied between −49% (reported as "slight increase in seizures") and 100% reduction, with a mean of 50.8% and a median of 55%. Study-wise, the mean reduction rates varied between 25% and 90%, with 55.03% on average (median: 45%).

No conclusions on tolerability of VNS in DS patients can be made from this analysis, as in some studies adverse events were not reported for DS sub-populations, were not systematically assessed or were not reported at all. However, hoarseness was the most frequently reported side-effect, which is in line with the majority of VNS trials in heterogeneous drug-resistant epilepsy populations [16,30].

## 4. Discussion

This meta-analysis finds adjunctive vagus nerve stimulation to elicit a ≥50% seizure frequency reduction in 55.9% of patients with DS with a median seizure frequency reduction of 55%. In comparison, the only class I study on an antiepileptic treatment in DS, which was a meta-analysis of two randomized-controlled trials carried out for Stiripentol found ≥50% seizure frequency reduction in 69% (23/33) of patients and an average seizure reduction of 70% [1,26]. However, comparing efficacy is problematic due to the fact that in the studies included in this meta-analysis many DS patients were receiving treatment with Stiripentol at initiation of VNS and throughout the VNS follow-up period. Furthermore the two randomized controlled trials of Stiripentol only assessed tonic or tonic-clonic seizures and may therefore be more comparable to the Fulton study (included in this analysis), which only assessed generalized tonic-clonic seizures and found a ≥50% reduction of this seizure type in 75% (9/12) of DS patients after ≥6 months of VNS therapy [19]. Considering the high SUDEP risk in patients with DS, assessing GTCS frequency may represent a clinically relevant strategy to quantify treatment effects, as GTCS frequency is the main risk factor for SUDEP [22]. Similarly the Orosz study that found a ≥50% seizure frequency reduction in 38% (5/13) of DS patients after VNS only assessed the "predominant seizure type" (defined as the most disabling seizure type determined by the physician but not necessarily the most frequent seizure type), but does not report which seizure type this was for each of the DS patients [29]. Generally however measuring reduction of the seizure type that impairs the patient most in daily life and functioning appears especially adequate in syndromic epilepsies such as DS or Lennox-Gastaut in which patients typically suffer from multiple seizure types of varying severity and frequency and rarely achieve complete seizure freedom. Adjusting treatment goals to attenuation, reduction or elimination of the most disabling seizure type while minimizing side-effects may represent achievable and individualized treatment goals that are meaningful to DS patients and their care-givers.

In this analysis 7 out 13 studies reported benefits of VNS beyond seizure frequency reduction such as cessation of status epilepticus, higher alertness or improved functioning and one may assume that these factors also strongly contribute to overall patient outcome. However this stands in contrast to the North American Consensus

Panel, which reached moderate consensus that VNS does not significantly benefit development or behavior in most DS patients. Improvement in quality-of-life metrics (e.g. QOLIE-89; CGI-I) and working memory associated with VNS have been demonstrated in heterogeneous drug-resistant epilepsy populations [17,33,39], however this has never been investigated in patients with DS.

Nevertheless one must interpret this analysis with caution as it is limited by the inherent property of meta-analyses of ignoring potentially important differences across studies as well as by the low sample sizes and low evidence class of studies included. This is however a general challenge for assessing treatments for rare-diseases and requires creative and innovative solutions.

## 5. Conclusion

This meta-analysis of 68 patients with Dravet Syndrome, finds adjunctive vagus nerve stimulation to be effective in reducing seizure frequency. Based on this preliminary analysis, controlled trials of VNS in this rare condition using patient-centric outcome measures are indicated.

## Conflict of interest

Maxine Dibué-Adjei is an employee of LivaNova PLC, manufacturer of vagus nerve stimulators. The other authors have no conflict of interest to disclose.

## Funding

This study was not funded by LivaNova PLC or by any other source.

## References

[1] Stiripentol (Diacomit): For Severe Myoclonic Epilepsy in Infancy (Dravet Syndrome) [Internet]. Canadian Agency for Drugs and Technologies in Health; 2015. . [Accessed 01, May 2017] https://www.ncbi.nlm.nih.gov/books/NBK349320/.
[2] Ali R, Elsayed M, Kaur M, Air E, Mahmood N, Constantinou J, et al. Use of social media to assess the effectiveness of vagal nerve stimulation in Dravet syndrome: a caregiver's perspective. J Neurol Sci 2017;375:146–9.
[3] Bremer A, Lossius MI, Nakken KO. Dravet syndrome—considerable delay in making the diagnosis. Acta Neurol Scand 2012;125:359–62.
[4] Caraballo RH. Nonpharmacologic treatments of Dravet syndrome: focus on the ketogenic diet. Epilepsia 2011;52(Suppl. 2):79–82.
[5] Cassé-Perrot CW, Wolff M, Dravet C. Neuropsychological aspects of severe myoclonic epilepsy in infancy. The neuropsychology of childhood epilepsy. New York: Plenum Press/Kluwer Academic; 2001. p. 131–40.
[6] Cersosimo RO, Bartuluchi M, Fortini S, Soraru A, Pomata H, Caraballo RH. Vagus nerve stimulation: effectiveness and tolerability in 64 paediatric patients with refractory epilepsies. Epileptic Disord 2011;13:382–8.
[7] Chen CY, Lee HT, Chen CC, Kwan SY, Chen SJ, Hsieh LP, et al. Short-term results of vagus nerve stimulation in pediatric patients with refractory epilepsy. Pediatr Neonatol 2012;53:184–7.
[8] Chiron C, Dulac O. The pharmacologic treatment of Dravet syndrome. Epilepsia 2011;52(Suppl. 2):72–5.
[9] Cooper MS, McIntosh A, Crompton DE, McMahon JM, Schneider A, Farrell K, et al. Mortality in dravet syndrome. Epilepsy Res 2016;128:43–7.
[10] Dlouhy BJ, Miller B, Jeong A, Bertrand ME, Limbrick Jr. DD, Smyth MD. Palliative epilepsy surgery in Dravet syndrome-case series and review of the literature. Childs Nerv Syst 2016;32:1703–8.
[11] Dravet C. Les epilepsies graves de l'enfant. Vie Médicale 1978;8:543–8.
[12] Dravet C. The core Dravet syndrome phenotype. Epilepsia 2011;52(Suppl. 2):3–9.
[13] Dravet C, Oguni H. Dravet syndrome (severe myoclonic epilepsy in infancy). Handb Clin Neurol 2013;111:627–33.
[14] Dravet CB, Oguni H, Fukuyama Y, Cokar O, Guerrini R. Dravet Syndrome (severe myoclonic epilepsy in infancy). Epileptic Syndromes in Infancy, Childhood and Adolescence. UK: John Libbey Eurotext Ltd.; 2012. p. 125–56.
[15] Dressler A, Trimmel-Schwahofer P, Reithofer E, Muhlebner A, Groppel G, Reiter-Fink E, et al. Efficacy and tolerability of the ketogenic diet in Dravet syndrome—comparison with various standard antiepileptic drug regimen. Epilepsy Res 2015;109:81–9.
[16] Elliott RE, Morsi A, Kalhorn SP, Marcus J, Sellin J, Kang M, et al. Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. Epilepsy Behav 2011;20:57–63.
[17] Englot DJ, Hassnain KH, Rolston JD, Harward SC, Sinha SR, Haglund MM. Quality-of-life metrics with vagus nerve stimulation for epilepsy from provider survey data. Epilepsy Behav 2017;66:4–9.
[18] Fernandez L, Gedela S, Tamber M, Sogawa Y. Vagus nerve stimulation in children less than 3 years with medically intractable epilepsy. Epilepsy Res 2015;112:37–42.
[19] Fulton SP, Van Poppel K, McGregor AL, Mudigoudar B, Wheless JW. Vagus nerve stimulation in intractable epilepsy associated with SCN1A gene abnormalities. J Child Neurol 2017;32:494–8.
[20] Gross RA, Johnston KC. Levels of evidence: taking neurology to the next level. Neurology 2009;72:8–10.
[21] Hanaya R, Niantiarno FH, Kashida Y, Hosoyama H, Maruyama S, Otsubo T, et al. Vagus nerve stimulation for genetic epilepsy with febrile seizures plus (GEFS+) accompanying seizures with impaired consciousness. Epilepsy Behav Case Rep 2017;7:16–9.
[22] Harden C, Tomson T, Gloss D, Buchhalter J, Cross JH, Donner E, et al. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2017;88:1674–80.
[23] Harkin LA, McMahon JM, Iona X, Dibbens L, Pelekanos JT, Zuberi SM, et al. The spectrum of SCN1A-related infantile epileptic encephalopathies. Brain 2007;130:843–52.
[24] Helmers SL, Duh MS, Guerin A, Sarda SP, Samuelson TM, Bunker MT, et al. Clinical and economic impact of vagus nerve stimulation therapy in patients with drug-resistant epilepsy. Epilepsy Behav 2011;22:370–5.
[25] Kang HC, Hwang YS, Kim DS, Kim HD. Vagus nerve stimulation in pediatric intractable epilepsy: a Korean bicentric study. Acta Neurochir 2006;99 (Suppl):93–6.
[26] Kassai B, Chiron C, Augier S, Cucherat M, Rey E, Gueyffier F, et al. Severe myoclonic epilepsy in infancy: a systematic review and a meta-analysis of individual patient data. Epilepsia 2008;49:343–8.
[27] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
[28] Ogino T, Ohtsuka Y, Yamatogi Y, Oka E, Ohtahara S. The epileptic syndrome sharing common characteristics during early childhood with severe myoclonic epilepsy in infancy. Jpn J Psychiatry Neurol 1989;43:479–81.
[29] 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.
[30] Panebianco M, Rigby A, Weston J, Marson AG. Vagus nerve stimulation for partial seizures. Cochrane Database Syst Rev 2015 [CD002896].
[31] Ragona F, Brazzo D, De Giorgi, Morbi M, Freri E, Teutonico F, et al. Dravet syndrome: early clinical manifestations and cognitive outcome in 37 Italian patients. Brain Dev 2010;32:71–7.
[32] 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.
[33] Ryvlin P, Gilliam FG, Nguyen DK, Colicchio G, Iudice A, Tinuper P, et al. The long-term effect of vagus nerve stimulation on quality of life in patients with pharmacoresistant focal epilepsy: the PuLsE (Open Prospective Randomized Long-term Effectiveness) trial. Epilepsia 2014;55:893–900.
[34] Scheffer IE, Zhang YH, Jansen FE, Dibbens L. Dravet syndrome or genetic (generalized) epilepsy with febrile seizures plus? Brain Dev 2009;31:394–400.
[35] Shahwan A, Bailey C, Maxiner W, Harvey AS. Vagus nerve stimulation for refractory epilepsy in children: more to VNS than seizure frequency reduction. Epilepsia 2009;50:1220–8.
[36] Sirisi DK, Arnold ST. Vagal nerve stimulation: is it effective in children with dravet syndrome? J Pediatr Epilepsy 2016;5:7–10.
[37] Skluzacek JV, Watts KP, Parsy O, Wical B, Camfield P. Dravet syndrome and parent associations: the IDEA League experience with comorbid conditions, mortality, management, adaptation, and grief. Epilepsia 2011;52(Suppl. 2):95–101.
[38] Spatola M, Jeannet PY, Pollo C, Wider C, Labrum R, Rossetti AO. Effect of vagus nerve stimulation in an adult patient with Dravet syndrome: contribution to sudden unexpected death in epilepsy risk reduction? Eur Neurol 2013;69:119–21.
[39] Sun L, Perakyla J, Holm K, Haapasalo J, Lehtimaki K, Ogawa KH, et al. Vagus nerve stimulation improves working memory performance. J Clin Exp Neuropsychol 2017;1–11.
[40] Trimmer JS, Rhodes KJ. Localization of voltage-gated ion channels in mammalian brain. Annu Rev Physiol 2004;66:477–519.
[41] Wirrell EC, Laux L, Donner E, Jette N, Knupp K, Meskis MA, et al. Optimizing the diagnosis and management of dravet syndrome: recommendations from a north american consensus panel. Pediatr Neurol 2017;68(18–34):e13.
[42] Wu YW, Sullivan J, McDaniel SS, Meisler MH, Walsh EM, Li SX, et al. Incidence of dravet syndrome in a US population. Pediatrics 2015;136:e1310–1315.
[43] Zamponi N, Passamonti C, Cappanera S, Petrelli C. Clinical course of young patients with Dravet syndrome after vagal nerve stimulation. Eur J Paediatr Neurol 2011;15:8–14.