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# Combined use of the ketogenic diet and vagus nerve stimulation in pediatric drug-resistant epilepsy

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## Abstract

**Objective:** Patients with drug-resistant epilepsy (DRE) pose considerable management challenges for patients, their families, and providers. Both the vagus nerve stimulator (VNS) and the ketogenic diet (KD) have been shown to be safe and effective in treating DRE. Nevertheless, information is lacking regarding treatment with combination of both modalities. This study reports the efficacy and tolerability of combining VNS and KD in a pediatric cohort with intractable epilepsy.

**Methods:** This is a retrospective review of 33 patients (0-17 years) with DRE treated with VNS and KD at a single pediatric level IV epilepsy center. We compared seizure reduction rates for each patient at baseline and at every clinic visit for 24 months after adding the second nonpharmacological therapy. The frequency of adverse events on the combined therapy was collected to assess safety and tolerability.

**Results:** There were a total of 170 visits for all patients while on the combined therapy. At 88% (95% CI: 83%-93%) of the visits, patients reported some reduction in seizure frequency. The proportion of patients reporting a greater than 50% seizure reduction over all visits was 62% (95% CI: 55%-69%). The proportion of a patient's visits with at least a greater than 50% reduction in seizure frequency had a median of 71% (IQR 33%-100%). Continued improvement was seen over time of combined treatment; for every one-unit time unit change (one month), there was a 6% increase in the odds of having a reduction in seizure frequency of >50% (OR = 1.06, 95% CI: 1.01-1.11).

**Significance:** This study shows that combining the VNS and KD in patients with drug-resistant epilepsy is well tolerated and reduces seizure frequency more than either one modality used alone and that the benefits in terms of seizure reduction continue to increase with the length of treatment.

## KEYWORDS

epilepsy surgery, neuromodulation, safety & efficacy, seizure control

Ayman T. Abdelmoity and Jean-Baptiste Le Pichon Contributed equally to the work.

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## 1 | INTRODUCTION

The prevalence of epilepsy in the United States is around 1% of the population.<sup>1</sup> In a 30-year longitudinal study of patients with newly diagnosed epilepsy, about 30% of the patients continued to have seizures despite having been treated with three or more antiepileptic drugs (AED).<sup>2</sup> The International League Against Epilepsy (ILAE) defines “drug-resistant epilepsy (DRE) “as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom”.<sup>3</sup> The burden of DRE is significant. In a survey of adult patients with epilepsy in 19 states in the USA, those with active epilepsy were more likely than those with inactive epilepsy to be unemployed, have lower income, be overweight, develop diabetes, have a stroke, and have mental health issues.<sup>1</sup> The burden of DRE is a challenge to patients, their families, and physicians. Recurrent seizures, prolonged seizure duration, and seizure severity are multiple factors that affect the burden of DRE.<sup>4</sup> DRE is also associated with multiple comorbid conditions including depression, anxiety, sleep disorder, and cognitive disabilities.<sup>5–9</sup> All of these conditions have a significant impact on quality of life. Patients with DRE are at higher risk of injuries, including falls, fractures, and other health complications related to seizures.<sup>5–7</sup> Multiple studies have shown an increase in healthcare utilization by patients with drug-resistant epilepsy, leading to increasing overall costs of treatment.<sup>10–12</sup> In addition, several quality of life metrics (ability to work, pursuit of higher education and ability to socialize) are affected by epilepsy and its comorbidities as well as the side effects of AEDs.<sup>5–9</sup> Patients with drug-resistant epilepsy are at higher risk for Sudden Unexplained Death in Epilepsy (SUDEP).<sup>13</sup> While becoming seizure-free is not likely for most patients with drug-resistant epilepsy, treatment goals aim at reduction in seizure burden (seizure frequency, severity, and duration), maximizing adherence and increasing treatment tolerability.<sup>14</sup>

If it is an option, resective epilepsy surgery is the treatment of choice for DRE. However, there are limitations to surgery. There are no practice guidelines for the use of surgery in pediatric epilepsy. In 2006, the International League Against Epilepsy<sup>15</sup> acknowledged that there was not enough class 1 evidence to create practice guidelines, rather they published a set of criteria for the surgical management of children with DRE. Resection of an epileptogenic focus is not always possible. Underlying generalized etiologies, genetic causes, epileptic foci numbers, and primality to eloquent cortex are some of many reasons resection surgery might not be optimal. While corpus callosotomy and multiple subpial transection can be considered, they are at best palliative and have limited objective evidence of efficacy. However, per the ILAE criteria, VNS should be considered after a careful surgical evaluation. The ketogenic diet is an alternative nonpharmacological

### Key Points

- Combined VNS and ketogenic diet therapy in the treatment of children with drug-resistant epilepsy is well tolerated.
- Combined therapy appears to provide synergistic benefits when compared to either therapy alone.
- The benefits of combined treatments continue to increase over the duration of treatment.

treatment for DRE. In 2018, the International Ketogenic Diet Study Group recommended that the diet should be a consideration for children who have failed two AEDs or more and for children with certain epilepsy syndromes.<sup>16</sup> It follows that both VNS and the ketogenic diet are important alternative treatments in children with DRE. Finally, these interventions are not mutually exclusive as almost 50% of patients with DRE do not have complete seizure remission after their resective surgery.<sup>17</sup> Both responsive neurostimulation (RNS) and deep brain stimulation (DBS) are FDA-approved in patients 18 years and older, while VNS is approved for patients four years and older. For RNS, the median reduction in seizure frequency was 44% at one year and 53% at two years.<sup>18</sup> Adverse events include implant site pain (15.7%), headache (10.5%), procedural headache (9.4%), dysesthesia (6.3%), simple partial seizures (6.3%), and complex partial seizures (5.8%).<sup>19</sup> For DBS, the seizure reduction was 41% at one year and 69% at 5 years.<sup>20</sup> Both the ketogenic diet (KD) and the vagus nerve stimulator (VNS) have been shown to be effective and safe in reducing seizure burden as well as improving quality of life for patients with DRE.

The KD consists of a high fat diet with limited carbohydrate and protein intake. It has been established as an efficacious method of treating both adults and children with pharmacologically resistant epilepsy.<sup>21</sup> The KD has also been reported to improve quality of life in patients with epilepsy, especially with regard to speech development and cognition.<sup>22</sup> Under normal metabolism, glucose is the main source of energy for the brain. During fasting and with the KD, fatty acids undergo beta oxidation and are converted into ketone bodies (acetoacetic acid, beta-hydroxybutyric acid, and acetone) that cross the blood-brain barrier and serve as an alternate source of energy for the brain.<sup>23</sup> The exact antiepileptic mechanism of action for the KD is not totally understood. Some of the postulated mechanisms of action, based on animal models, include augmenting the production of  $\gamma$ -aminobutyric acid (GABA),<sup>24</sup> modulation of the GABA receptors,<sup>25</sup> and prevention of kindled seizures.<sup>26</sup>

Multiple studies have shown the VNS to be safe and effective in the treatment of drug-resistant epilepsy.<sup>27</sup> It is

approved by the FDA for treatment of patients 4 years and older with focal onset drug-resistant epilepsy.<sup>28</sup> The exact mechanism of action of the VNS is not completely understood. Several studies have shown that the VNS can increase the neurotransmitters norepinephrine,<sup>29–31</sup> GABA,<sup>32–34</sup> and serotonin<sup>33,35</sup> and decrease aspartate,<sup>33,35</sup> ultimately suppressing epileptiform activity. VNS has also been reported to increase cerebral blood flow<sup>36,37</sup> and desynchronize EEG rhythms.<sup>38,39</sup>

To date, there have been few studies examining the effectiveness of combining both KD and VNS in treating patients with DRE. In 2007, Kossoff et al published a retrospective chart review of 30 patients from six institutions who were on combination VNS and KD treatment.<sup>40</sup> The children were followed over 12 months after combination therapy was started, and half were still on combination therapy at the end of the study. Twenty-three children (77%) had >50% seizure reduction from baseline (before combination therapy). At 12 months, 15 patients were still on combination therapy. Of those, five (33%) had >90% seizure reduction, seven (47%) had 50%-90% reduction, and none were seizure-free. Since this study, there has not been any other report of the effectiveness of combined VNS and KD treatment in DRE. The aim of this study was to assess the value of combining both the KD and VNS in patients with drug-resistant epilepsy who did not meet satisfactory seizure control on either modality alone.

## 2 | METHODS

This is a retrospective study at a single level 4 epilepsy center at a free-standing children's hospital (Children's Mercy Kansas City). Institutional Review Board (IRB) approval was obtained prior to enrolling patients and collecting data. A consent was obtained from patients and/or their legal guardians prior to participation in the study. Patients included were 0-17 years old, had DRE as defined by the International League Against Epilepsy (ILAE),<sup>3</sup> and were treated with combined VNS and KD. Data collected included patients' demographics, epilepsy type, seizure history, side effects, seizure medications, and seizure reduction after initiating the combination therapy. Seizure response was measured as: no change, less than 50% improvement, more than 50% improvement, more than 90% improvement, or seizure-free as compared to previous treatment (VNS or KD alone). Time points studied included baseline (defined as three-month time period before addition of second nonpharmacological modality), the first postintervention visit at 1 month, and visits at every three-month interval thereafter for 24 months. Patients were considered to respond if their seizures improved by 50% or more compared to baseline (while on either therapy alone).

Descriptive statistics such as medians, interquartile ranges (IQR), and proportions were used to summarize the

**TABLE 1** Changes in seizure frequency for all visits combined

Change in Seizures, 170 total visits	n (%)
No change	20 (11.8)
≤50% reduction	45 (26.5)
>50% reduction	64 (37.7)
>90% reduction	27 (15.9)
Seizure-free	14 (8.2)

data. 95% confidence intervals for proportions are reported. Generalized estimating equations were used to do repeated measures analyses on dichotomous outcomes. SAS, version 9.4 (SAS Institute Inc, Cary, NC), was used for all statistical analyses.

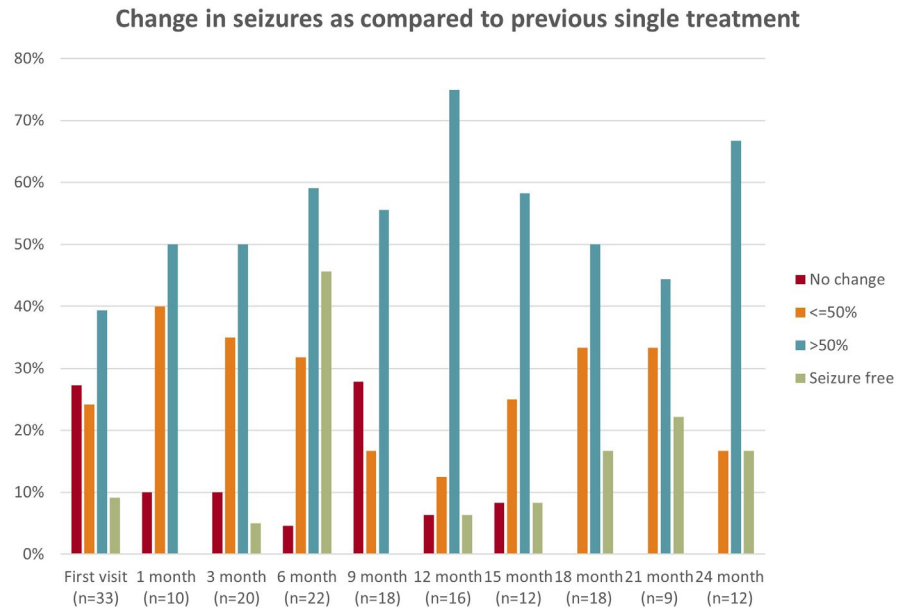
## 3 | RESULTS

There were 33 consecutive patients included in this study. Of those, 17 were male and 16 were female. The mean age at enrollment was 5.22 years (SD 4.42 years, range 0.25-14.42 years). Average age at seizure onset was 1.09 years (SD 1.35 years, 0-4.91 years). There were a total of 170 visits for all patients while on the combined treatment. The mean number of visits per patient was 5 (SD 2) with a minimum of 1 and a maximum of 9 visits.

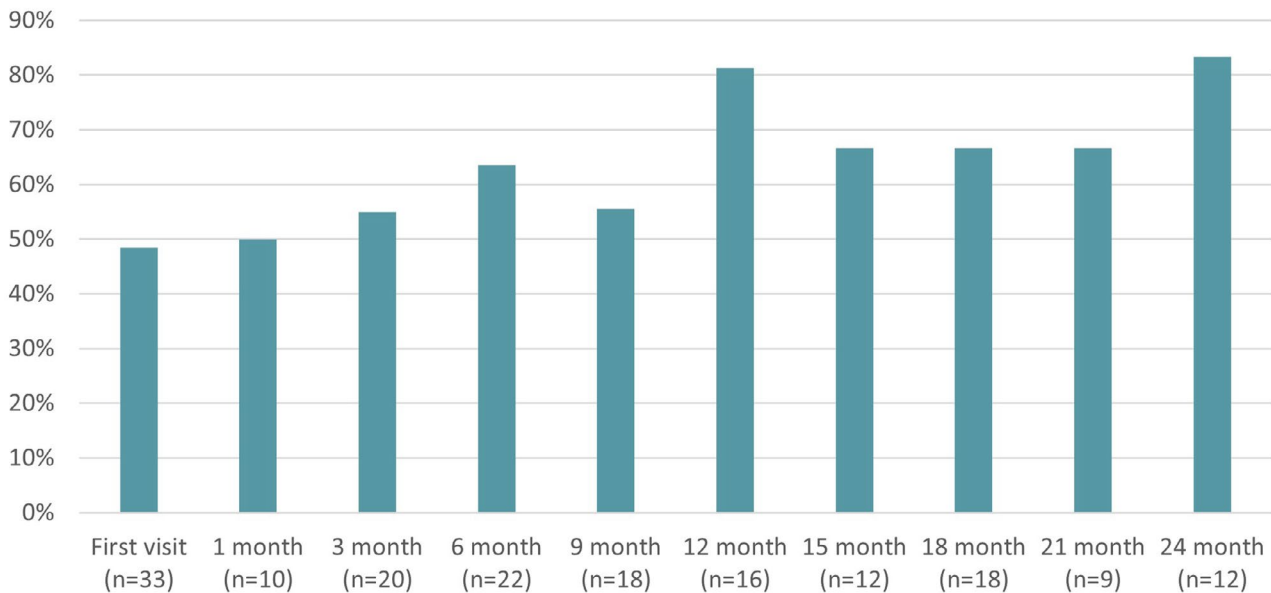
Of all the patient visits, no change in seizure frequency was reported at 20 visits (11.8%, 95% CI: 6.9%-16.6%; Table 1), while patients or families reported some reduction in seizure frequency in 150 visits (88.2%, 95% CI: 83.3%-93.1%). The proportion of patient visits reporting a greater than 50% seizure reduction was 61.8% (95% CI: 54.5%-69.1%). For each patient, we looked at outcomes over all of their visits and calculated the percent of visits where that person had some reduction and also the percent of visits with at least a greater than 50% reduction. The proportion of a patient's visits with at least a greater than 50% reduction in seizure frequency had a median of 71% (IQR 33.3%-100%). The median percentage of visits with some reduction was 100% with an IQR of 77.8%-100%.

When the data were plotted by date of visit postcombined therapy, the benefit derived from treatment appeared to increase with time (Figure 1). With the exception of the first visit that was attended by all the patients (following initiation of the second treatment modality), each time point visit was attended by a subset of patients, varying from 9 to 22 patients. The time of follow-up visit varied, but each patient had an average of 5 visits over the 24 months (SD 2.1). Several trends were notable. The number of patients showing no change in seizure frequency was relatively low (10%-30%), and there were no patients reporting no improvement after the 15-month visit. Conversely, the number of seizure-free patients steadily rose over the course of the treatment and

**FIGURE 1** Change in seizure frequency with time. These data represent 33 patients for a 24-mo follow-up. The number of visits included at each time point is noted below the time headings. Note that “first visit” is the first visit after being on the combined treatment



**Proportion of visits with >50% reduction in seizures are compared to previous single treatment**



**FIGURE 2** Proportion of visits with at least 50% seizure reduction: The data have been dichotomized to >50% reduction (includes seizure-free) and <=50% reduction. Generalized estimating equations were used to do a repeated measures analysis on this dichotomous outcome. The odds of having a reduction of >50% change over time was significant ( $P = 0.0250$ )

seemed to stabilize between 15% and 20% of the patient visits at the 18-months visit. Similarly, the number of patients with >50% seizure reduction also steadily increased over time, stabilizing by the 12-month visit to approximately 70% (adding the >50% seizure reduction and the seizure-free patients).

We then dichotomized the reduction in seizure frequency at each visit to at least a >50% reduction (includes seizure-free) vs. ≤50% reduction (Figure 2). Generalized

estimating equations were used to do a repeated measures analysis on this dichotomous outcome. The change over time was significant ( $P = 0.025$ ). The odds ratio for a one-unit change (one month) is 1.06 (95% CI: 1.01, 1.11). Thus, for every one-month increase of time on the combined treatment the odds of having a reduction of >50% increase by 6%. When looking at a 3-month increase of time, the odds ratio of a more than 50% reduction is 1.19 (95% CI: 1.02, 1.38).



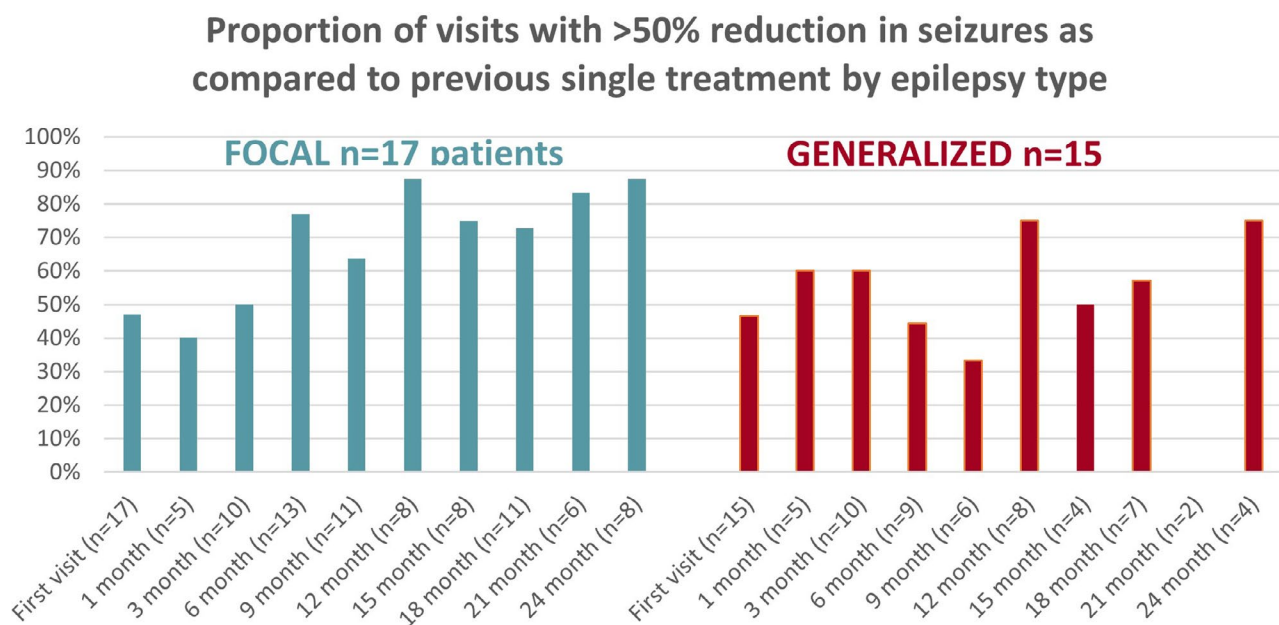
We looked for a differential response to combined treatment by including the type of epilepsy (focal or generalized) in the repeated measures model (Figure 3). One patient was excluded from this analysis due to having a mixed epilepsy. We found no significant difference in the response to treatment between epilepsy type ( $P = 0.407$ ). We also wanted to know whether the order in which the nonpharmacological modalities were added made a difference in the overall response to the combined treatment (Figure 4) and we found no significant difference ( $P = 0.216$ ). Finally, differences according to gender were tested and no significance was found ( $P = 0.057$ ).

Side effects while on the combined treatments were mostly gastroenterological or renal in nature (GI: constipation, flatulence, emesis, acid reflux; renal: osteopenia, osteoporosis, renal tubular acidosis, kidney stones; Table 2). Complications were reported in at least one visit for 18 (54.6%) patients, and 38 of the total 170 visits (22%) reported at least one complication. None of these complications resulted in discontinuation of either of the KD or the VNS.

## 4 | DISCUSSION

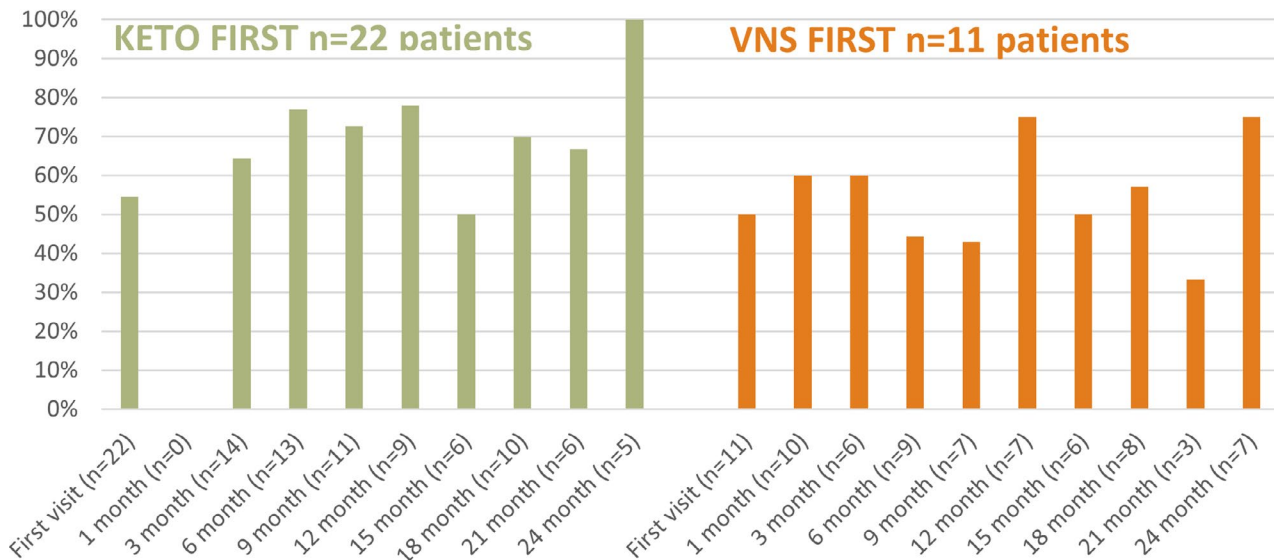
This is a retrospective chart review of 33 patients who were treated with a combination of VNS and KD. We wanted to ascertain whether the combined treatment modality was superior to either modality alone. In total, we had 170 visits on the combined treatment. There were 5 possible responses for

the outcome variable: no change,  $\leq 50\%$  reduction,  $>50\%$  reduction, 90% reduction, and seizure-free. Table 1 shows the percent breakdown for each response. Of the 170 visits, 105 (62%) reported greater than 50% seizure reduction compared to either modality alone. When reduction in seizure frequency was plotted over the time visit (Figure 1), the response to the combined therapy showed a continued improvement with time. Notably, there are no patients reporting no changes after 15 months of combined treatment. We then dichotomized the data into  $>50$  and  $<50\%$  seizure reduction (Figure 2). The odds of having a having a  $>50\%$  reduction significantly increased by 6% for each one-month time increment. This confirms a continued improvement in seizure reduction over time when on the combined therapy. No differences were found in type of epilepsy and order in which the second treatment modality was added confirming that the combined therapy was equally effective at treating generalized and focal epilepsies and that the order of introduction had no effect. One might expect that the side effects on the combined therapy would be additive, adding a significant burden to the combined treatment. In our analysis, the combined therapy was well tolerated. While over half (54.6%) of the patients reported at least one side effect at one of their clinic visits, the side effects were well tolerated, and no patient had either therapy discontinued due to side effects. We found that renal and gastrointestinal side effects were the most common complaints with approximately one-third of the patient having a side effect in each of these categories. Kossoff et al reported a multicenter (six centers) retrospective study of 30 children on



**FIGURE 3** Proportion of visits with  $>50\%$  seizure reduction by seizure type. One patient had a mixed epilepsy (both focal and generalized) and was excluded from the analysis. The number of patients in each group is noted at the top of the graph, and the bottom indicates how many patients had visits at each time point. The variable for epilepsy type was included in the repeated measures model and made no difference in terms of the odds of having a reduction of  $>50\%$  ( $P = 0.4067$ )

### Proportion of visits with >50% reduction in seizures as compared to previous single treatment, by previous single treatment



**FIGURE 4** Proportion of visits with >50% reduction by therapy started first. When the data were separated by the type of therapy introduced first, the difference in terms of the number of visits with >50% seizure reduction was not significantly different between the two groups ( $P = 0.2164$ )

**TABLE 2** Complications

Complications, n = 33 pts	n (%)
Any Complications	18 (54.6)
GI	11 (33.33)
Renal	9 (27.3)
Neurological	2 (6.1)
Metabolic	4 (12.1)
Cardiac	1 (3)

the combination therapy.<sup>40</sup> In that paper the authors showed that at the first month of combined therapy, 62% of their patients had at least a 50% seizure reduction; at 3 months, this number grew to 70%. Interestingly, none of their patients reported side effects from the combined therapy. However, 13 of the 30 patients discontinued combined therapy due to lack of efficacy. In our study, no patient dropped out, and virtually, all patients demonstrated some reduction in seizure frequency (the median percentage of visits with some reduction was 100%, IQR of 77.8%-100%). These differences between the two studies may relate to the consistency of treatment paradigm we have developed at our center over the years as opposed to the potential lack of consistency in a multicenter study as was reported in the Kossoff et al study. Which therapy was initiated first, VNS or KD, did not make a difference in either study. We also analyzed response to the combined

treatment according to epilepsy type, focal versus generalized. Here we did not find any significant difference either. This is consistent with other publications that have shown that both the VNS and the KD are effective in focal and generalized seizures.<sup>41-43</sup> The management of DRE is complex and almost always involves polypharmacy. Polypharmacy has been associated with worse quality of life in patients with epilepsy despite seizure control.<sup>44</sup> Alternatives to polypharmacy are therefore an important tool for epileptologists when managing children with DRE. While both VNS and the KD have been shown to be effective treatments when used alone, we show that combination of the two treatments provides further benefits, is generally well tolerated, and continues to improve over time.

Our study has limitations. First and foremost, this is a retrospective study. The nature of the study makes it vulnerable to both selection bias and recollection bias. In this study, we used as a control group the patients at baseline on either therapy alone before introduction of the second nonpharmacological intervention. This method cannot control for changes that may occur over time in each patient. Nevertheless, these results add more evidence that combined VNS and KD therapy is effective and generally well tolerated in the treatment of DR epilepsy. Furthermore, we show that improvements continue over time up to 24 months. This is the largest study of combined therapy done in children with DR epilepsy in any one single



center. This observation adds convincing evidence that combination VNS and KD therapy is a good alternative for patients with drug-resistant epilepsy and should be considered, especially on patients on multiple antiepileptic drug treatments.

## 5 | CONCLUSION

The management of patients with DRE is a challenge for both the treating physicians and patients and their families. The goal of treatment is usually simplifying polypharmacy while decreasing seizure frequency and severity. The use of combined KD and VNS therapy over either therapy alone yields significant reduction in seizure frequency and is generally well tolerated. Furthermore, this study shows a synergistic effect when between these nonpharmacological interventions, with a continuing improvement in the seizure reduction over time. While larger prospective studies will be useful in solidifying these findings, the data presented herein add evidence that combined VNS and KD therapy is an effective treatment and may provide better seizure control for children with DRE.


## CONFLICTS OF INTEREST

Ahmed Abdelmoity received honoraria for consulting or serving on the speaker bureau for Livanova, UCB, and Greenwich. The remaining authors have no conflicts of interest. No external funding received for the work presented. All coauthors have been substantially involved in the study and the preparation of the manuscript; no undisclosed groups or persons have had a primary role in the study and/or preparation of the manuscript; all coauthors have seen and approved the submitted version of the paper and accept responsibility for its content. The work described herein is consistent with the Journal's guidelines for ethical publication.

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