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RESEARCH PAPER

Fish oil (n-3 fatty acids) in drug resistant epilepsy: a randomised placebo-controlled crossover study

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ABSTRACT

Background n-3 fatty acids inhibit neuronal excitability and reduce seizures in animal models. High-dose fish oil has been explored in two randomised trials in drug resistant epilepsy with negative results. We performed a phase II randomised controlled crossover trial of low-dose and high-dose fish oil in participants with drug resistant epilepsy to explore whether low-dose or high-dose fish oil reduces seizures or improves cardiovascular health.

Methods Randomised placebo-controlled trial of low-dose and high-dose fish oil versus placebo (corn oil, linoleic acid) in 24 participants with drug resistant epilepsy. A three-period crossover design was utilised lasting 42 weeks, with three 10-week treatment periods and two 6-week washout periods. All participants were randomised in double-blind fashion to receive placebo, high dose or low dose in different sequences. The primary outcome was per cent change in total seizure frequency.

Findings Low-dose fish oil (3 capsules/day, 1080 mg eicosapentaenoic acid+docosahexaenoic acid) was associated with a 33.6% reduction in seizure frequency compared with placebo. Low-dose fish oil was also associated with a mild but significant reduction in blood pressure. High-dose fish oil was no different than placebo in reducing seizures or improving cardiac risk factors.

Interpretation In this phase II randomised crossover trial, low-dose fish oil was effective in reducing seizures compared with placebo. The magnitude of improvement is similar to that of recent antiepileptic drug trials in drug resistant epilepsy (DRE). The results indicate that low-dose fish oil may reduce seizures and improve the health of people with epilepsy. These findings justify a large multicentre randomised trial of low-dose fish oil (n-3 fatty acids <1080 mg/day) in drug resistant epilepsy.

Trial registration number NCT00871377.

INTRODUCTION

Drug resistant epilepsy is a serious disease, defined as failure of a patient with epilepsy to respond to two or more appropriate antiepileptic drugs at a therapeutic dose.[1] Treatment options include adding new antiepileptic drugs, followed by consideration of epilepsy surgery, neuromodulation or dietary therapy (ketogenic diet or the modified Atkins diet).[1–4] Fish oil, which contains ω-3 fatty acids (*n-3 fatty acids*), is of particular interest because it may improve cardiac health, reduce sudden cardiac death after myocardial infarction and delay the onset of seizures in a pentylenetetrazole model of acute seizures.[5 6] n-3 fatty acids, especially docosahexaenoic acid (DHA), cross the blood brain barrier and become incorporated into the cell membrane's lipid bi-layer.[5] There, n-3 fatty acids are believed to modify calcium and sodium channels, reducing membrane excitability in heart myocytes and neurons.[7 8] Randomised controlled clinical trials of high-dose fish oil have been performed with promising, yet inconclusive results.[9 10] The purpose of this clinical trial is to evaluate high-dose and low-dose fish oil in a phase II randomised placebo-controlled crossover trial in participants with drug resistant epilepsy.

METHODS

Study design

The study design is a prospective, randomised, three-period crossover clinical trial of two doses of fish oil: low dose, high dose or placebo, in participants with drug resistant partial-onset seizures (simple partial, complex partial or secondary generalised tonic–clonic seizures). The study design is summarised in figure 1.

Since all participants are on placebo during one of the three periods, there is no placebo pretreatment period. All treatment comparisons for efficacy are between treatment with fish oil (high or low dose) and placebo. This strategy was chosen to reduce the total duration of the trial, which is already long at 42 weeks. For vital signs, heart rate variability (HRV) and laboratory measures, visit 1 serves as the pretreatment baseline.

The intervention was Pharmavite 'Nature Made' fish oil capsules. Each fish oil capsule contained 216 mg of eicosapentaenoic acid (EPA) and 144 mg of DHA, for a total of 360 mg n-3 fatty acids per capsule. The low-dose group received a total n-3 dose=1080 mg/day (three fish oil capsules per day) and the high-dose group received a total n-3 dose=2160 mg/day (three fish oil capsules twice a day). The placebo was a capsule identical in appearance, taste and odour containing corn oil (no EPA or DHA), equal to three corn oil capsules twice a day. Corn oil was selected as a placebo since it is ubiquitous in the American diet, and has no antiepileptic effect.[11] All three capsules were administered in gel form orally, twice a day. To maintain blind interactions, the low-dose group received three fish oil capsules and three corn oil capsules per day, to keep the number of capsules the same between groups. An independent laboratory certified that the study drug contained no polychlorinated biphenyl (PCBs) or heavy metals (certificate of analysis on file, principal investigator).

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A

Study Flow				
Treatment Period A Ten Weeks	Washout 6 weeks	Treatment Period B Ten Weeks	Washout 6 weeks	Treatment Period C Ten Weeks
Low		High		Placebo
Placebo		Low		High
High		Placebo		Low

B

	Possible Treatment Allocations and Sequences
P L H	Placebo, then Low Dose, then High Dose
P H L	Placebo, then High Dose, then Low Dose
L H P	Low Dose, then High Dose, then Placebo
L P H	Low Dose, then Placebo, then High Dose
H L P	High Dose, then Low Dose, then Placebo
H P L	High Dose, then Placebo, then Low Dose

Figure 1 (A) Study flow. (B) Possible treatment allocations and sequences.

The study was funded by a research grant from the National Institutes of Health/National Center for Complementary and Alternative Medicine (NCCAM). An investigational new drug application (IND) was obtained from the US Food and Drug Administration (FDA) prior to initiation of the study. Signed informed consent was obtained from the participants at the time of enrolment. The study was registered at clinicaltrials.gov (NCT00871377).

Participants were evaluated in the UCLA General Clinical Research Center on enrolment, and at the beginning and end of each 10-week treatment period. A period of 6 weeks duration occurred between each treatment period to allow the effects of the study intervention to washout before beginning a new treatment period. The total study duration for each participant was 42 weeks (figure 1).

On entry, and at the beginning of each treatment period, vital signs, history, physical examination, Chalfont Seizure Severity Scale, 1 h cardiac Holter monitoring for HRV, complete blood count, chemistry panel, lipid panel and C reactive protein were obtained. Seizure calendars were reviewed and validated by the study physician at each visit. No medication changes were allowed during the study unless absolutely needed for participant safety.

Inclusion and exclusion criteria

The inclusion criteria required for study entry were as follows: male or female, age 18–70; history of drug resistant localization-related partial onset or generalised tonic/clonic seizures defined according to the International League Against Epilepsy (ILAE) classification: specifically, a history compatible with localisation-related or partial epilepsy, and an EEG and/or a MRI of the brain consistent with a localisation-related or partial epilepsy; three or more simple partial, complex partial or tonic–clonic seizures per month; evidence of at least three seizures per month for at least 2 months prior to the study; prior exposure to at least three antiepileptic drugs in therapeutic doses or concentrations alone or in combination at least one trial of two concurrent antiepileptic drugs at therapeutic doses or concentrations; concurrent therapy with at least one antiepileptic drug at therapeutic doses or concentrations.

The exclusion criteria were as follows: significant or progressive medical, cardiac or other illness; allergy to fish products or fish oil; history of a coagulation disorder; history of non-epileptic seizures; consumption of fish oil at any time 30 days or less prior to enrolment; any change in antiepileptic drugs for 30 days or fewer prior to enrolment; treatment with warfarin or daily aspirin for 30 days or fewer prior to enrolment; previous poor compliance with therapy; alcohol or drug misuse; uncountable seizures as a result of seizure clustering, or inadequate supervision if the patient could not count their own seizures.

Randomisation

Participants were randomised in blocks of four to a crossover sequence of low dose, high dose and placebo. All participants were randomised once they met inclusion criteria at visit 1, and entered the initial 10-week treatment period. Entry into the study was followed by a 6-week washout period, and again a 10-week treatment period, followed by a second 6-week washout period, and then a final 10-week treatment period. Participants were randomised to six possible sequences (see figure 1). The entire duration of the study was 42 weeks.

Statistical analysis

Seizures were obtained from participant seizure calendars, and calculated in seizures per day for each treatment period, then computed as seizures per month, where a month is defined as 28 days. Repeated-measure models for crossover designs were used to compare seizure rates or means. The model included a treatment effect (treatment 1, 2 or 3), period effect (A, B or C) and treatment×period interaction (non-parallelism), and allowed for the non-independence (correlations) of multiple observations from the same patient.

Study design and primary outcome measure

The *primary end point* was per cent change in total seizure frequency for low-dose fish oil or high-dose fish oil versus placebo. Total seizure frequency was defined as the total number of countable and stereotyped simple partial, complex partial and generalised tonic/tonic–clonic seizures. The null hypothesis was that the per cent change in seizure frequency during treatment with fish oil was not different from placebo.

Data for the primary outcome, total seizure frequency, conformed to a negative binomial distribution. Therefore, a repeated-measure negative binomial model was used to compare seizure frequency rates using maximum likelihood to compute p values. For secondary outcomes (mean arterial pressure (MAP), heart rate, Chalfont Seizure Severity Scale, measures of HRV (including RMSSD, SDNN, SDANN), lipids, C reactive protein), examination of quantile plots indicated that the residual errors for the secondary outcomes conformed to Gaussian (normal) distributions. Therefore, the conventional parametric mixed-model repeated-measure analysis of variance (ANOVA) was used to compare means and compute p values for these outcomes. For SDNN, SDAAN, RMSSD, pulse and MAP, results were determined following subtraction of the initial baseline only, and, in a separate analysis, subtraction of the 'local' baseline at the start of each period (visit 1, visit 4, visit 7). For total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides, there was no local baseline at visit 4. A participant was considered to have a 50% reduction in seizure rate under low dose if the seizure rate under low dose was at least 50%

lower than the seizure rate under placebo, regardless of treatment period order. The same definition applied to the high-dose treatment condition.

RESULTS

Participant characteristics

Table 1 summarises the clinical data of the participant cohort. The average age of the participants was 33 years, SD 10.33. Sixteen participants were women, and eight participants were men. Forty-six participants were screened for the study; 25 met criteria and were enrolled. Twenty-four participants received at least one dose of the study medication. Figure 2 shows the CONSORT flow diagram for the study.

Primary end point: per cent change in total seizure frequency

The average seizure frequency during low-dose fish oil treatment was 12.18 (SE 2.72) vs 17.67 seizures/month (SE 4.56) for high-dose fish oil, and 18.34 seizures/month (SE 4.28) for placebo. The difference in seizure frequency between low-dose fish oil and placebo was −33.6%, p=0.02. Seizure frequency under high-dose fish oil was similar to that of placebo, with no significant difference between high dose and placebo, p=0.82. Low-dose fish oil was associated with a 31% reduction in seizure frequency compared with high-dose fish oil (borderline significant, p=0.05).

For low-dose fish oil, 5/20 (25%) experienced a 50% reduction in seizures compared with placebo. Three of 20 (15%) exposed to high-dose fish oil experienced a 50% reduction in seizures compared with placebo. Two participants were seizure free during treatment with low-dose fish oil (2/20, 10%). No participants were seizure free during treatment with placebo or high-dose fish oil (all comparisons, p=0.22–0.48, Fisher exact test). Table 2 summarises the data for the primary and key secondary efficacy outcomes.

Low-dose fish oil was associated with an average reduction of 1.95 mm Hg (SE=1.91 mm Hg) in MAP from baseline, which was significantly less than high-dose fish oil (1.84 mm Hg average increase, SE=1.90 mm Hg, p=0.03), but similar to the effect of the placebo (2.31 mm Hg decrease, SE=1.89 mm Hg, p=0.83, ANOVA). For the low-dose fish oil treatment, there was a trend towards improved high-frequency HRV (RMSSD +4.97 ms, p=0.09; RMSSD is a measure of the integrity of vagus nerve control of the heart). Fish oil was not associated with significant improvements or changes in heart rate, HRV, lipids (total cholesterol, HDL, LDL or triglycerides) or Seizure Severity Score. Table 2 summarises the major primary and secondary findings of the study.

Adverse events

Fish oil was well tolerated, with no serious adverse events encountered during the study. One participant died during the study due to autopsy-confirmed sudden death in epilepsy (SUDEP). This participant was in the high-dose fish oil treatment period when SUDEP occurred. At the same time, the participant was on multiple antiepileptic drugs and aripiprazole, an antipsychotic also associated with an increase in cardiac mortality. The patient had failed epilepsy surgery, vagal nerve stimulation, had frequent tonic–clonic seizures and was found after a seizure next to his bed in the prone position. The cause of death was thought by the investigator to be unrelated to the treatment with fish oil.

Table 1 Summary of participant clinical data

N	Age	Sex	Type	Duration (years)	Number of AED's	Localisation	Aetiology	Baseline seizure frequency
1	32	M	CPS, GTC	14	3	TLE, bilateral	Head trauma	3/month
2	28	F	CPS, GTC	7	2	TLE, bilateral	Encephalitis	
3	56	F	SPS	44	2	TLE, right	Unknown	5/month
4	44	M	SPS, CPS, GTC	33	1	TLE, left	Febrile	6/month
5	37	M	SPS	15	3	Left occipital	Unknown	300/month
6	32	M	SPS, CPS, GTC	31	2	Non-localised	Febrile illness	3/month
7	24	M	SPS	10	2	L temporal	Unknown	12/month
8	45	M	CPS, GTC	45	4	R parietal	Cortical dysplasia	6/month
9	28	F	LGS DROP, MYOCLONIC GTC	28	2	Bilateral	LGS, translocation X chromosome	20/month
10	19	M	SPS, GTC	5	3	Bilateral	Unknown	60/month
11	22	F	SPS CPS	12	3	Right temporal	Unknown	4/month
12	37	F	CPS	7	2	Right temporal	Unknown	5/month
13	18	F	CPS, GTC	17	3	Non-localised	Unknown	24/month
14	30	M	CPS, GTC	22	4	Bilateral	Hypoxic ischaemia birth injury	Unknown
15	40	F	CPS	34	2	Right temporal	Familial TLE	
16	32	F	SPS, GTC	10	1	Temporal lobe	Unknown	10/month
17	34	F	SPS, CPS, GTC	29	3	Non-localised	Birth injury	5/month
18	42	F	SPS, CPS	30	2	Bilateral temporal	Unknown	30/month
19	46	F	SPS, CPS,	31	2	Left temporal	Ganglioglioma	3/month
20	28	F	SPS, GTC	20	1	Unknown	Head trauma	8/month
21	30	M	SPS, CPS, GTC	26	3	Left temporal	Birth injury	15/month
22	21	M	CPS, GTC	16	4	Unknown	Cortical dysplasia	60/month
24	22	F	SPS, CPS,	17	1	Unknown	Unknown	10/month
25	53	F	CPS	13	2	Bitemporal	Unknown	13/month

AED, antiepileptic drug; CPS, complex partial seizures; GTC, generalized tonic clonic seizures; LGS, Lennox Gastaut syndrome; SPS, simple partial seizures; TLE, temporal lobe epilepsy.

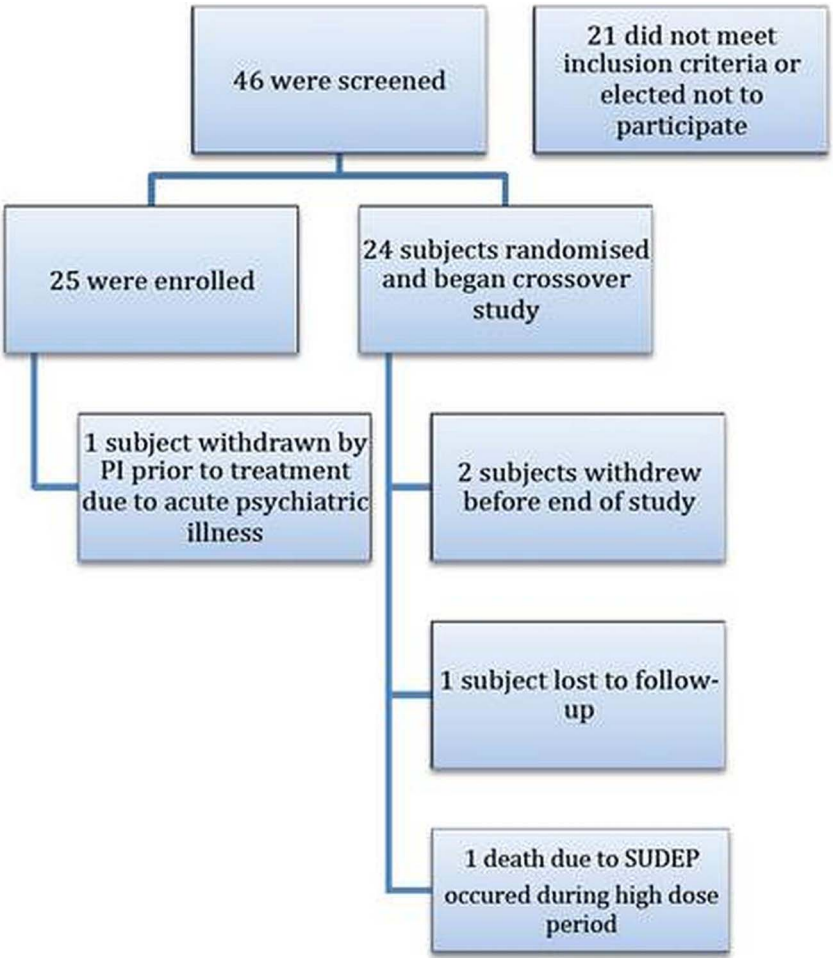

Figure 2 CONSORT flow diagram. PI, principal investigator; SUDEP, sudden death in epilepsy.

DISCUSSION

The primary finding is that low-dose fish oil (3 capsules/day, 1080 mg of EPA+DHA) was associated with a reduction in seizure frequency of −33.6% compared with placebo. Low-dose fish oil was associated with a responder rate of 25% and a seizure-free rate of 10%. Though the size of the trial will require confirmation, the magnitude of the effect on seizure frequency is similar to many randomised trials of antiepileptic drugs.[2]

Low-dose fish oil was also associated with a modest reduction in blood pressure, but this finding was significant only when compared with high-dose fish oil. The reduction in blood pressure indicates that low-dose fish oil may exert a positive cardiovascular benefit in this cohort with drug resistant epilepsy, a finding of some importance, given the recent data that the risk of death due to myocardial infarction is significantly higher in people with epilepsy.[12]

To date, there have been two major randomised controlled trials of n-3 fatty acids for epilepsy, both of which used higher doses. In 2005, Yuen *et al*[9] first reported a randomised placebo-controlled parallel trial of fish oil for epilepsy in 58 participants with epilepsy, in which 1700 mg of EPA+DHA was

Table 2 Summary of efficacy data—means or proportions

	Fish oil 3 capsules/day 1080 mg n-3 FAs/day	Fish oil 6 capsules/day 2160 mg n-3 FAs /day	Placebo corn oil	p Value*
Seizures/month	12.18* SE 2.72	17.67 SE 4.56	18.34 SE 4.28	*0.02
Seizure, per cent change from placebo	−33.6%*	−3.6%	–	*0.02
Responder rate	25% SE 9.7%	15% SE 8.4%	NA	NS
Seizure-free rate	10.0%	0%	0%	NS
Mean change blood pressure from pretreatment visit 1 (MAP, mm Hg)	−1.95 SE 1.91	+1.84 SE 1.90	−2.31 SE 1.89	<0.03, Low dose vs high dose
High-frequency heart rate variability, RMMSD Mean change from pretreatment visit 1 (milliseconds)	+4.97 SE 2.95	+1.18 SE 2.91	−0.41 SE 2.85	0.09, Low dose vs placebo

SEs are in parenthesis. Low dose comparison to placebo unless otherwise indicated.
*refers to the difference between low dose fish oil and placebo.
FA, fatty acid; MAP, mean arterial blood pressure; NA, not applicable; NS, not significant.

administered daily. No side effects or antiepileptic drug interactions were reported. Initially, a significantly higher number of participants on fish oil experienced a greater than 50% reduction in seizures in the first 6 weeks of the treatment period; however, over the entire 12-week treatment period, there was no significant difference in responder rate for the treatment versus control.[9] Between-group differences in seizure frequencies at baseline may have made it difficult to detect true differences, a phenomenon common in epilepsy clinical trials.[9] In 2008, Bromfield *et al*[10] reported a randomised controlled trial in 21 participants with drug resistant epilepsy using a higher dose of fish oil (2200 mg/day of EPA and DHA). During the acute treatment period, fish oil supplementation was associated with an increased seizure frequency of 6% versus a reduction of 12% with placebo.[10] However, after conclusion of the 12-week randomised trial, long-term treatment was associated with significant reductions in seizures, with 5/19 participants experiencing a 50% reduction in seizures, many of whom (4/5) were originally randomised to placebo.[10]

Fish oil is safe and well tolerated. The US FDA designates fish oil at doses of 3 g/day as 'Generally Recognized as Safe' (GRAS).[13] Recently, plasma n-3 fatty acid levels (not fish oil supplementation) have been associated with an increased risk of prostate cancer.[14] This finding is controversial, as dietary sources of n-3 fatty acids include smoked fish, high in nitrates and nitrites, well known to increase the risk of prostate cancer.[15] Recently, a large trial found that fish oil consumption in later life is protective against prostate cancer.[15] More research on the link between n-3 fatty acids and prostate cancer is needed.

Data from several large well-executed double-blind studies have shown that fish oil supplementation or a diet high in n-3 fatty acids reduce mortality after myocardial infarction.[5 6 16] These data have led the American Heart Association to issue the following statement:

> Evidence from prospective secondary prevention studies suggests that EPA and DHS supplementation ranging from 0.5 to 1.8 g/d (either as fatty fish oil supplements) significantly reduces subsequent cardiac and all cause mortality.[16]

The large GISSI Prevenzioni study showed that n-3 fatty acids at 1150 mg/day (similar to our low dose of 1060 mg/day) significantly reduced mortality and sudden cardiac death compared with placebo.[6] Similarly, Singh *et al*[17] demonstrated that a higher dose of n-3 fatty acids (2 g EPA/DHA/day) significantly reduced cardiac-related deaths after myocardial infarction at 1 year by nearly 50%. Recently, a meta-analysis and interventional trial of fish oil failed to demonstrate a consistent reduction in cardiovascular risk.[18 19] However, a large prospective study of multiethnic Americans found a significant protective effect of fish oil intake, n-3 fatty acid levels and cardiovascular risk.[20] A second meta-analysis found that fish oil significantly reduces the risk of cardiovascular disease.[21] The authors note that the earlier meta-analysis included studies of very low dose n-3 fatty acids (<500 mg/day), which may have been subtherapeutic.[21] Given the conflicting studies, clarification of the role and optimum dose of fish oil in cardiovascular disease is needed.[18–21]

The lack of efficacy of high-dose fish oil in this trial is consistent with data from recent animal studies. Acute administration of high-dose n-3 fatty acids (DHA, 600 mg/kg) exacerbates seizures in a pentylenetetrazole model.[22] This is in direct contrast to lower doses of DHA (<400 mg/kg), which exhibit an anticonvulsant effect.[2] Similarly, rats, which are genetically resistant to seizures, experience a significant increase in susceptibility to kindling when exposed to high-dose fish oil (1000 mg/kg of EPA, 700 mg/kg of DHA).[23] The authors hypothesise that the increased susceptibility to high-dose n-3 fatty acids may be partially due to excessive reductions in non-esterified fatty acids (eg, arachidonic acid).[23]

The relative efficacy of low-dose fish oil compared with high-dose fish oil has also been reported in clinical trials in major depressive disorder.[24] Depressed participants experience significant improvements in mood following supplementation with low-dose n-3 fatty acids (1 g of EPA/day), but no improvement with high dose (2 or 4 g of EPA/day).[24] The response to fish oil at low dose for seizures and depression have substantial implications for use, given the common propensity for individuals to self-dose with 'a little helps, a lot should help much more' thought process. The dose–response findings also raise substantial implications for mechanisms of action, which must be better understood if fish oil interventions be considered for epilepsy.

It is important that the results from this trial be confirmed in a large multicentre trial. Limitations include the relatively short duration of exposure; participants were only exposed to each treatment for 10 weeks. It is unknown whether the improvement in seizures for the low-dose group is sustained over time. Second, due to the crossover design, a pretreatment baseline was not incorporated. This was designed to minimise the time where participants were held captive in the study without treatment, due to the already long duration of the study (42 weeks). However, since the study was a double-blind placebo-controlled crossover design, all comparisons were made to a true placebo. A large confirmatory study will likely use a traditional parallel group design with a pretreatment baseline.

Finally, the study did include three participants who had exclusively simple partial seizures. Inclusion of participants with partial seizures is common in antiepileptic drug studies. However, these participants were highly drug resistant, and their response did not contribute to efficacy demonstrated by fish oil, as none experienced more than a 17% reduction in seizures.

In summary, we report that low-dose fish oil (3 capsules/day, total of 1080 mg EPA+DHA) was associated with a 33.6% reduction in seizure frequency compared with placebo in a cohort with drug resistant epilepsy, and a mild but significant reduction in blood pressure. A large randomised controlled trial of fish oil is warranted to confirm or refute the findings of this study. Low-dose fish oil is a safe and low-cost intervention that may reduce seizures and improve cardiovascular health in people with epilepsy.

Contributors CMD is the guarantor. PRM played a key role in overall execution of study. RH helped PI to conceptualise the project and was involved in analysis of heart rate variability. LS and JS provided collaboration, evaluated patients, provided important clinical and cross-coverage service to the principal investigator. SM provided key collaboration for heart rate variability services. JG was involved in power and statistical analysis. The authors acknowledge and thank Marijo Clark and Pharmavite, Inc. for providing fish oil capsules and the placebo for this study.

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Competing interests CMD is a part time employee of NeuroSigma, a device company, which develops devices for epilepsy and other disorders.

Ethics approval Study approval was obtained from the NCCAM Office of Clinical Research, and the UCLA Office of Protection of Human Subjects.

Provenance and peer review Not commissioned; externally peer reviewed.

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