DRAVET Syndrome UK

Hope for families with life-limiting epilepsy

Parent/Carer & Professional Conference 2019

#DSUKLondon19

This Independent meeting is supported by an educational grant from GW Pharmaceuticals and Zogenix.
And also supported by XTX Markets

[XTX] MARKETS

New treatment algorithm & emerging treatments for Dravet Syndrome

Professor J Helen Cross OBE

Young Epilepsy

Great Ormond Street Hospital for Children NHS Trust

Great Ormond St Institute of Child Health UCL

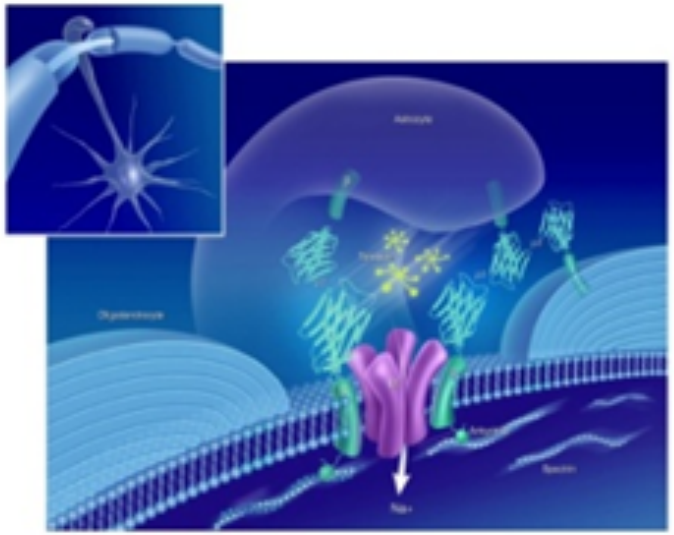
Epi CARE

European Reference Network for rare or low prevalence complex diseases

Network Epilepsies (ERN EpiCARE)

Outline

- Treatments used in Dravet syndrome
- What is the evidence?
- Where are we now?
- Newer agents on the horizon



Dravet syndrome
Tailored treatment

Effective anti-epileptic drugs

- **Valproate**
- **Clobazam**

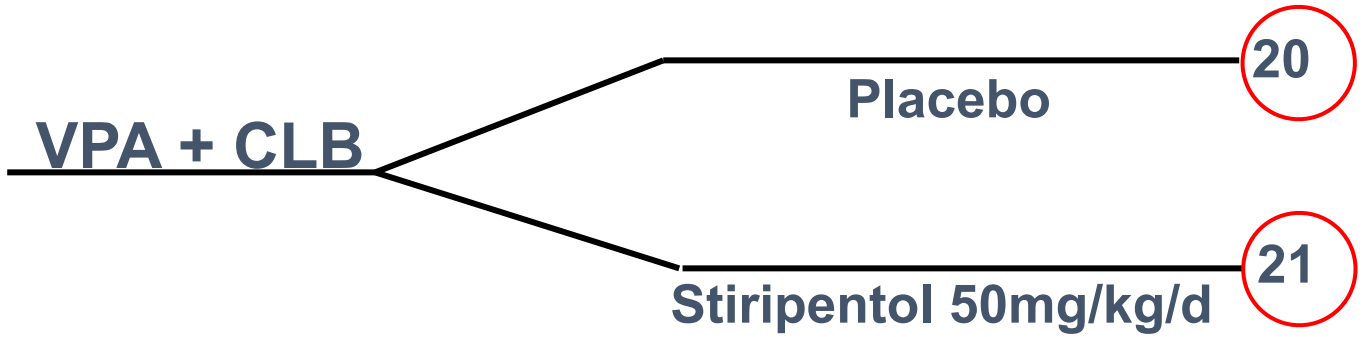
+/- Stiripentol

- **Topiramate**
- **Levetiracetam**
- **Ketogenic diet**

Seizure aggravation

- **Carbamazepine, phenytoin**
- **Lamotrigine - *Guerrini et al 1996***

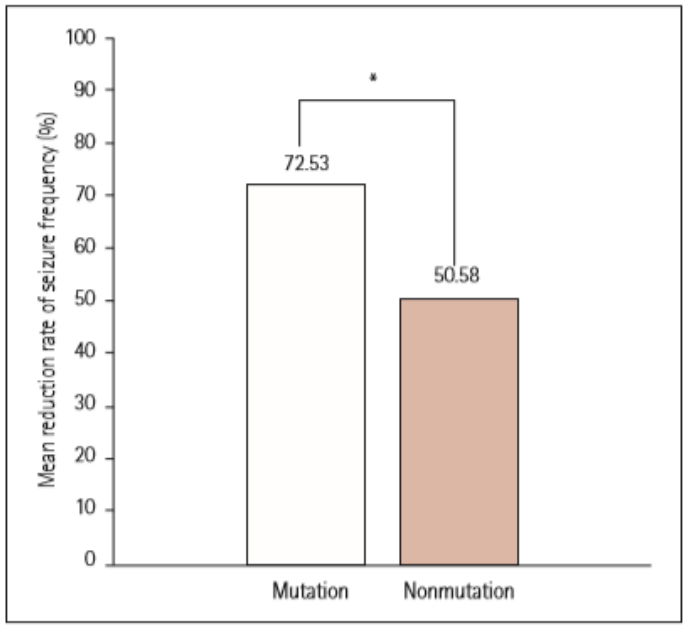
Dravet Syndrome
STP – Placebo controlled trial
STICLO France
(Chiron et al Lancet 2000;356:1638-42)



	Placebo	*Stiripentol*	*p*
Responders	5%	71%	<0.00002
Change seizure frequency	+ 7%	-70%	<0.002
Seizure free	0	9	

Efficacy of stiripentol with or without SCN1A mutation

- 32 children with Dravet syndrome
- 15 mutation, 17 no mutation
- efficacy of STP greater with mutation, specifically missense mutations



Cho et al J Clin Neurol 2018 Jan;14(1):22-28

Stiripentol use in adults

Balestrini & Sisodiya
Acta Neurol Scand 2017;135:73-79

- 13 adult subjects with DS (eight females, five males).
- Responder rate 3/13 (23%) at 36 months.
- Seizure exacerbation (3/13, 23%),
- no change (3/13, 23%),
- < 50% reduction in seizures (2/13, 15%),
- > 50% reduction in GTCS but no other seizure types (1/13, 8%),
- undefined response (1/13, 8%).
- Retention rate 62% at 12m, 31% at 5 years.
- Adverse effects 7/13 (54%):
  - anorexia,
  - weight loss,
  - unsteadiness
  - tiredness.
- Withdrawal 3/13 (23%).

lower responder rate and a similar tolerability profile.

Other medication

Topiramate Coppola et al Epilepsy Res 2002;49:45-48

- Open label add-on study
- 18 patients
- 10 >50% reduction, No aggravation
- Mild to moderate adverse events in 4 patients

Levetiracetam *Striano et al Neurology 2007;69:250-4*

- Open label add-on study
- Dravet syndrome >3 years old, 4 t/c/month
- F/up 6-36m
- Responders 64.2% for tonic-clonic, 60% myoclonic, 60% focal, 44.4% absence

Rufinamide *Mueller et al Epilepsy & Behavior 2011;21:282-4*

- Retrospective European multicentre
- 20 patients; responder rate at 6m 20%, after 34 m 5%
- Aggravation of seizures 30%, no effect 45%

Perampanel Yoshitomi et al Epilepsy Res 2019;154:34-38

- 10 patients, age 11.5+/- 2.2 yrs
- 5 >50% reduction in seizures; benefit early in introduction
- Responders GTC 50% (4/8), unilateral clonic : 50% (3/ 6), myoclonic : 33% (1/3), atypical absence : 33% (1/3), and focal impaired awareness seizure: 100% (1/1)
- Side effects in 7/10, mild

Bromide in Patients with *SCN1A*-Mutations Manifesting as Dravet Syndrome

Jan Lotte [1] Edda Haberlandt [2] Bernd Neubauer [3] Martin Staudt [1,4] Gerhard Josef Kluger [1,5]

Reduction of Seizure Frequency	After 3 Months	After 12 Months
Patients with bromide	32 (100%)	28 (88%)
All responders	26 (81%)	25 (78%)
Reduction 100%	10 (31%)	1 (3%)
Reduction 75–99%	2 (6%)	8 (25%)
Reduction 50–74%	6 (19%)	6 (19%)
Reduction <50%	2 (6%)	2 (6%)
Reduction unclear	6 (19%)	8 (25%)

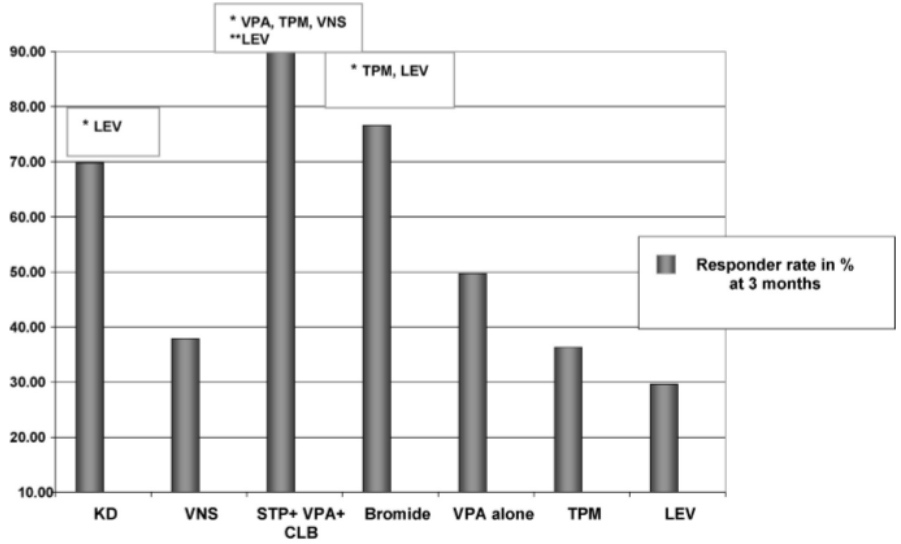
Reduction of Seizure Frequency	After 3 Months	After 12 Months
Patients with bromide	32 (100%)	28 (88%)
All responders	26 (81%)	25 (78%)
Reduction 100%	10 (31%)	1 (3%)

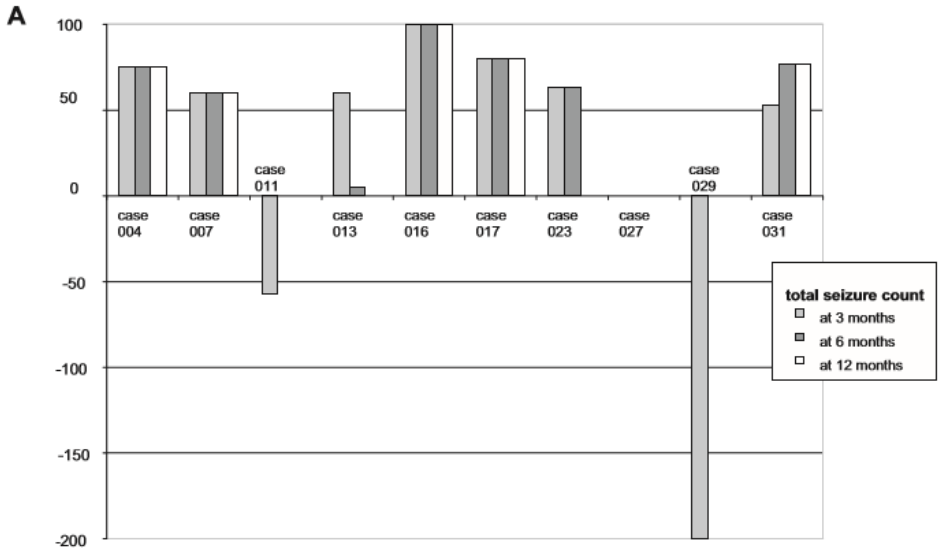
Ketogenic diet

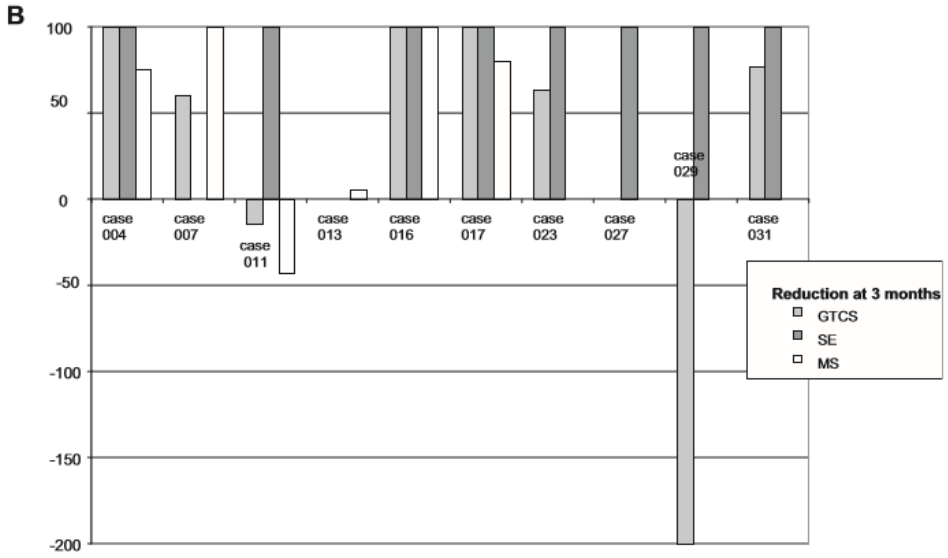
Efficacy and tolerability of the ketogenic diet in Dravet syndrome — Comparison with various standard antiepileptic drug regimen

Anastasia Dressler[a], Petra Trimmel-Schwahofer[a], Eva Reithofer[a], Angelika Mühlebner[a], Gudrun Gröppel[a], Edith Reiter-Fink[a], Franz Benninger[b], Roland Grassl[b], Martha Feucht[a,*]

Epilepsy Res 2015;109:81-9







Dravet syndrome

Treatment to avoid?

	Number of patients	No aggravated
Carbamazepine	28	16 (61%)
Vigabatrin	14	9 (64%)
Lamotrigine	12	8 (67%)
Phenobarbitone	23	6 (26%)

Thanh et al 2006

Epilepsia, 39(5):508–512, 1998
Lippincott–Raven Publishers, Philadelphia

Lamotrigine and Seizure Aggravation in Severe Myoclonic Epilepsy

Renzo Guerrini, *Charlotte Dravet, *Pierre Genton, Anna Belmonte, †Anna Kaminska, and †Olivier Dulac

*Institute of Child Neurology and Psychiatry, University of Pisa, Institute for Clinical Research Stella Maris Foundation, Calambrone, Pisa, Italy; *Centre Saint Paul, Marseille; and †Neuropédiatrie, Hopital Saint-Vincent-de-Paul, Paris, France.*

Medications reported to have reduced seizure frequency (five most common)	Number/total (%)
Valproate	81/160 (51)
Clobazam/clonazepam	55/160 (34)
Topiramate	45/160 (28)
Levetiracetam	21/160 (13)
Stiripentol	20/160 (13)

Medications reported to have increased seizure frequency (three most common)	Number/total (%)
Carbamazepine	36/60 (60)
Lamotrigine	26/60 (43)
Valproate	4/60 (7)

Brunklaus et al Brain 2012;135:2329-2336

21 children, SMEI, 3 centres

>50% increase in convulsive seizures 8

Aggravation of myoclonic seizures 18

Age dependent?

Dev Med Child Neurol 2015;57:200-2

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY CASE REPORT

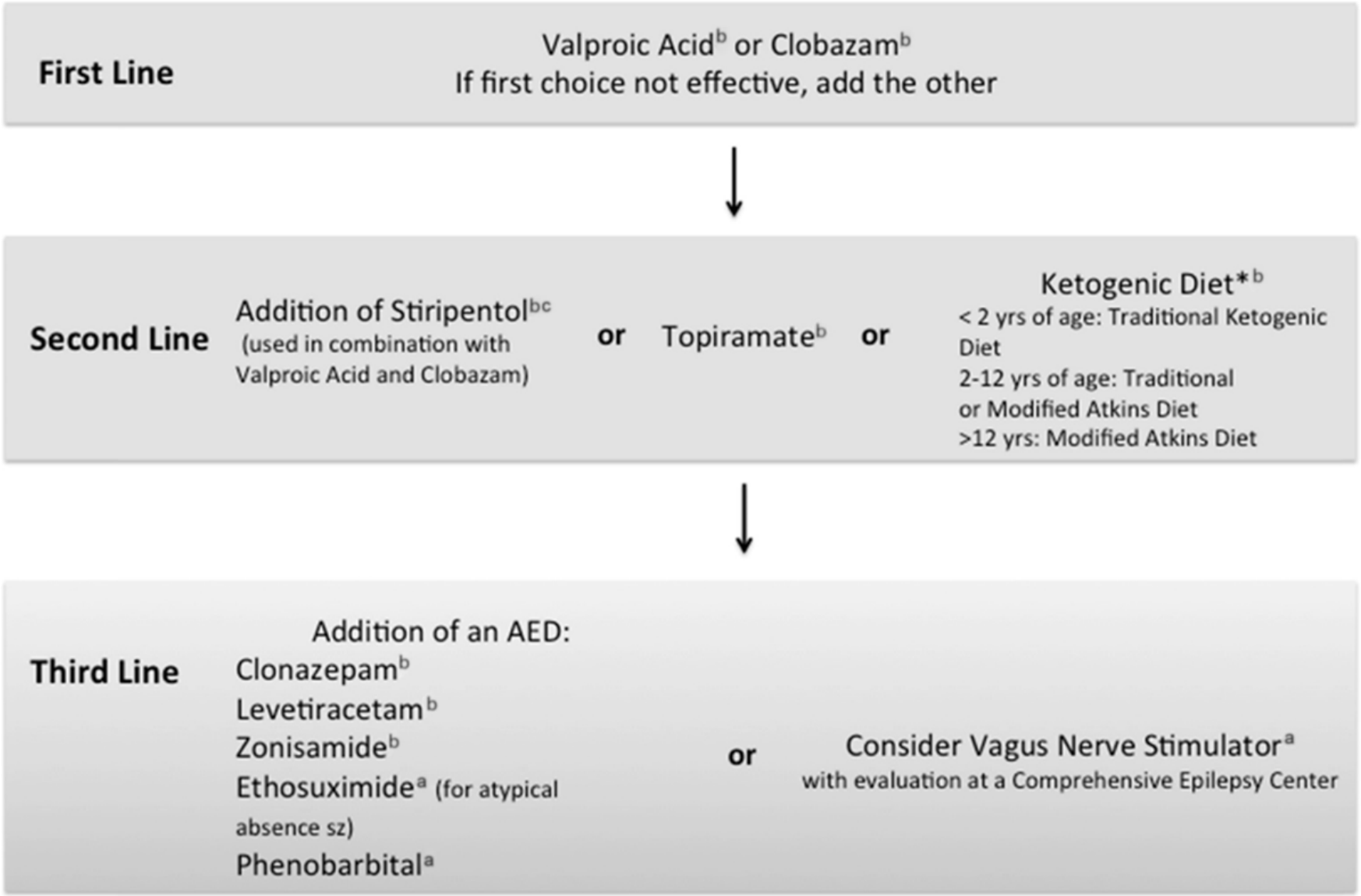
Lamotrigine can be beneficial in patients with Dravet syndrome

LINDA DALIC[1] | SAUL A MULLEN[1,2] | ELIANE ROULET PEREZ[3] | INGRID SCHEFFER[2,4]

1 Austin Health, Melbourne, Vic.; **2** Department of Medicine, Epilepsy Research Centre, Austin Health, The University of Melbourne, Melbourne, Vic., Australia. **3** Paediatric Neurology and Neurorehabilitation Unit, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland. **4** Department of Paediatrics, Royal Children's Hospital, The University of Melbourne, Melbourne, Vic., Australia.

Correspondence to Ingrid E Scheffer at Melbourne Brain Centre, 245 Burgundy St, Heidelberg, Vic. 3084, Australia. E-mail: i.scheffer@unimelb.edu.au

3 patients age 33, 27 and 14 years
Exacerbation of seizures n withdrawal of Lamotrigine



Wirrell EC, Laux L, Donner E et al Ped Neurol (Elsevier) 2017: 68:18-34.e3

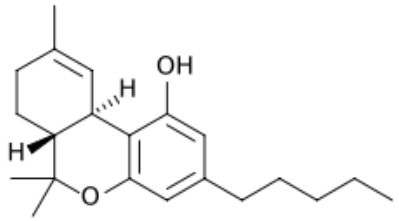
Practical aspects

- Prompt treatment of fever
- Avoidance of hyperthermia
- Awareness of triggers
  - Excitement
  - Photosensitivity?
- Prompt treatment of prolonged seizures

What about newer agents?

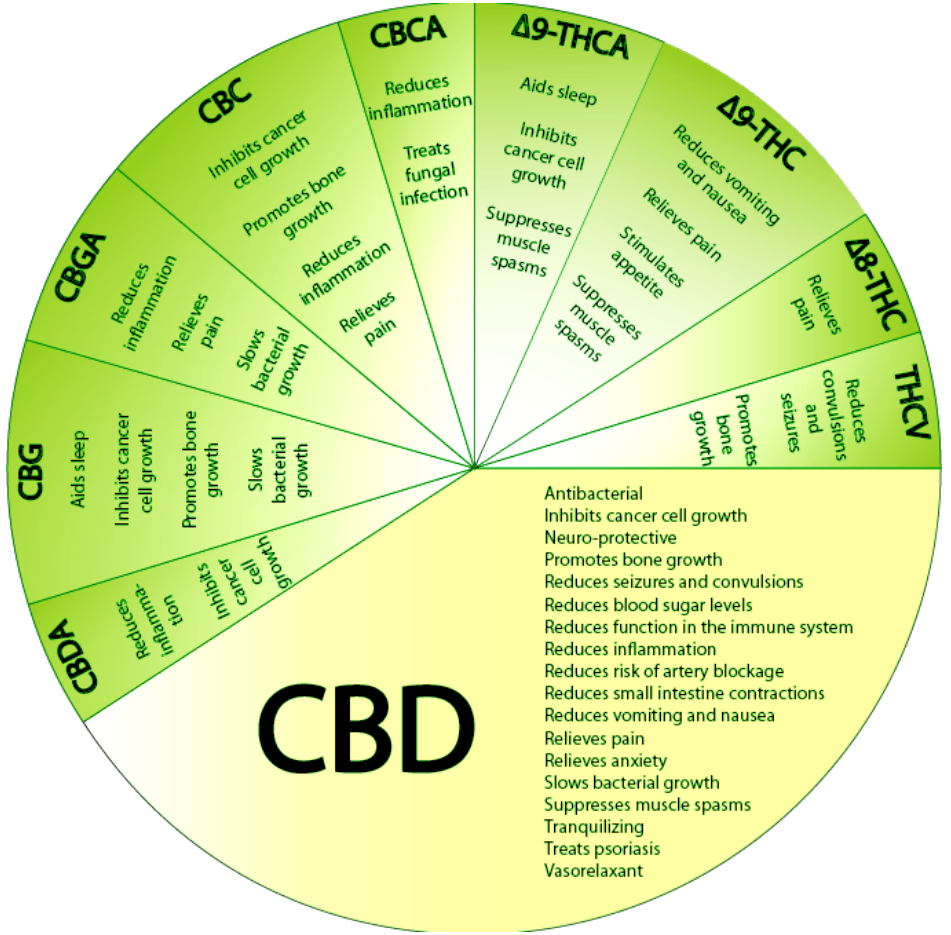
Cannabis

- **Cannabis: for the most part, *Cannabis sativa*.**
- **One of the most widely used recreational and medicinal drugs worldwide.**
  - **~150 million people smoking cannabis daily (WHO)**
- **Likely the first non-food plant cultivated by humans (~8000 BC)**
- **Best known for its psychoactive constituent, Δ^9-tetrahydrocannabinol ('THC').**



Applications

- Epilepsy
- Neuropsychiatric disorders
  - Anxiety
  - Schizophrenia
  - post-traumatic stress disorders
  - Anxiolytic
  - Antipsychotic
- Antiemetic
- Anti-inflammatory properties



Is there evidence for effect in epilepsy?

- **Large preclinical evidence base asserting mixed effects on seizures in animal models**

Compound	Species	Number of discrete conditions/models/ designs	Dose	Anticonvulsant	No effect	Proconvulsant
THC	6	31	0.25-200 mg/kg	61%	29%	10%*
CBD	2	21	1-400 mg/ kg	81%	19%	0%
Other plant cannabinoids	2	7	N/A	100%	0%	0%
CB1 receptor agonists	2	55	N/A	73%	18%	2% (7% mixed effect)

Whalley (2014) Cannabis and Seizures American Herbal Pharmacopeia

*Includes non-seizure studies where convulsions were reported (see next slide)

Its ‘natural’ – is it safe?

Cannabis use before age 15 and subsequent executive functioning

Maria Alice Fontes, Karen I. Bolla, Paulo Jannuzzi Cunha, Priscila Previato Almeida, Flávia Jungerman, Ronaldo Ramos Laranjeira, Rodrigo A. Bressan and Acioly L. T. Lacerda

The British Journal of Psychiatry (2011) 198, 442–447.

- **104 chronic cannabis,**
  - **49 early-onset users**
  - **55 late-onset users**
  - **44 controls**
- **No differences in IQ, vocabulary or block design**
- **The early-onset group had**
  - **more perseverative errors**
  - **completed fewer categories on the WCST.**
  - **performed poorly on STROOP**
  - **Poorer performance on the FAB**

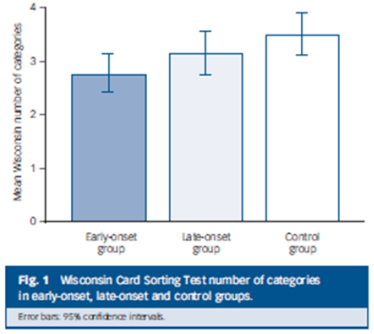


Fig. 1 Wisconsin Card Sorting Test number of categories in early-onset, late-onset and control groups.
Error bars: 95% confidence intervals.

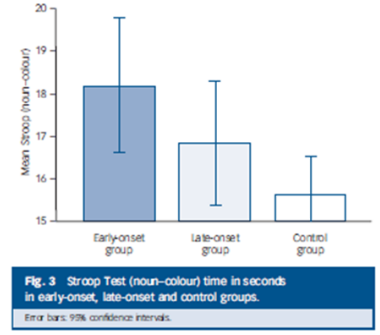


Fig. 3 Stroop Test (noun–colour) time in seconds in early-onset, late-onset and control groups.
Error bars: 95% confidence intervals.

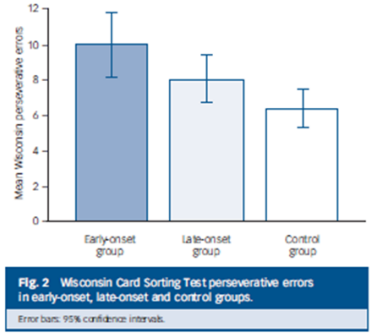


Fig. 2 Wisconsin Card Sorting Test perseverative errors in early-onset, late-onset and control groups.
Error bars: 95% confidence intervals.

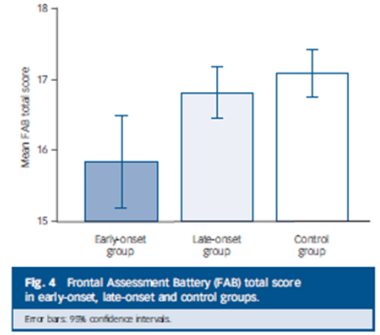
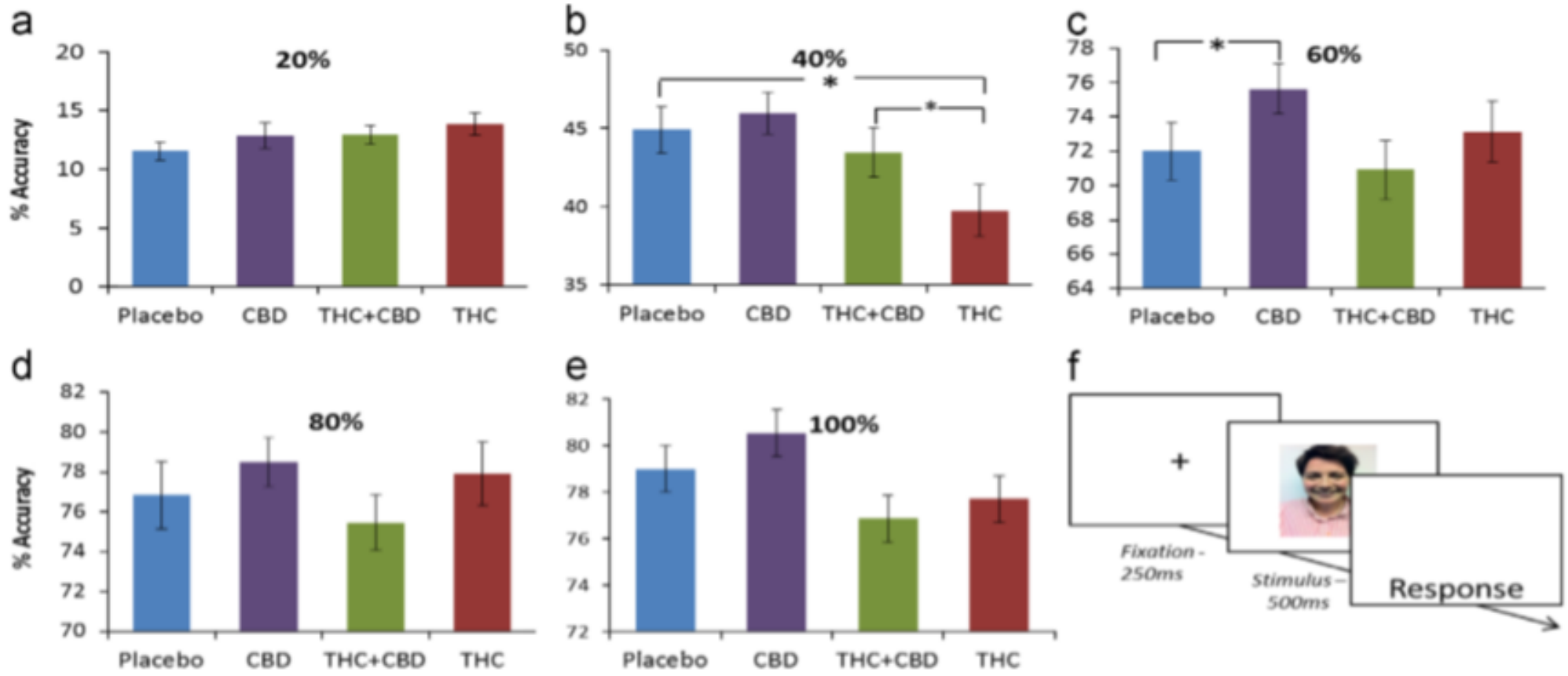


Fig. 4 Frontal Assessment Battery (FAB) total score in early-onset, late-onset and control groups.
Error bars: 95% confidence intervals.

Acute effects of delta-9-tetrahydrocannabinol, cannabidiol and their combination on facial recognition

Hindocha et al 2015



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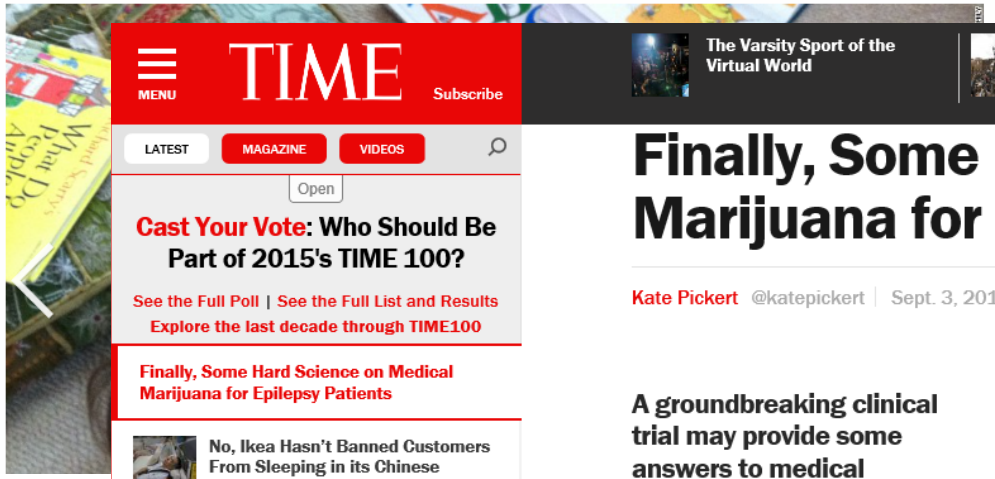
Marijuana stops child's severe seizu

By Saundra Young, CNN

Updated 2151 GMT (0451 HKT) August 7, 2013



The Marijuana Del

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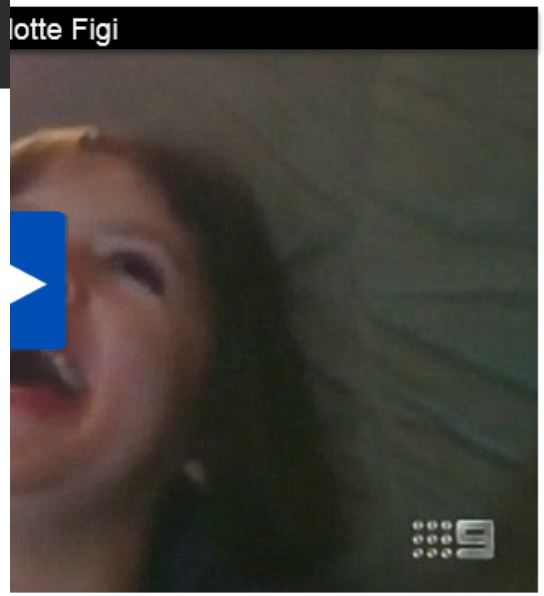

arijuana for Charlotte

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Finally, Some Hard Science on Medical Marijuana for Epilepsy Patients

No, Ikea Hasn't Banned Customers From Sleeping in its Chinese Stores

This Doggie Photo Booth Is the Cutest Thing You'll See Today

The Varsity Sport of the Virtual World

Caught in the Cross Fire

Finally, Some Hard Science on Medical Marijuana for Epilepsy Patients

Kate Pickert @katepickert | Sept. 3, 2014

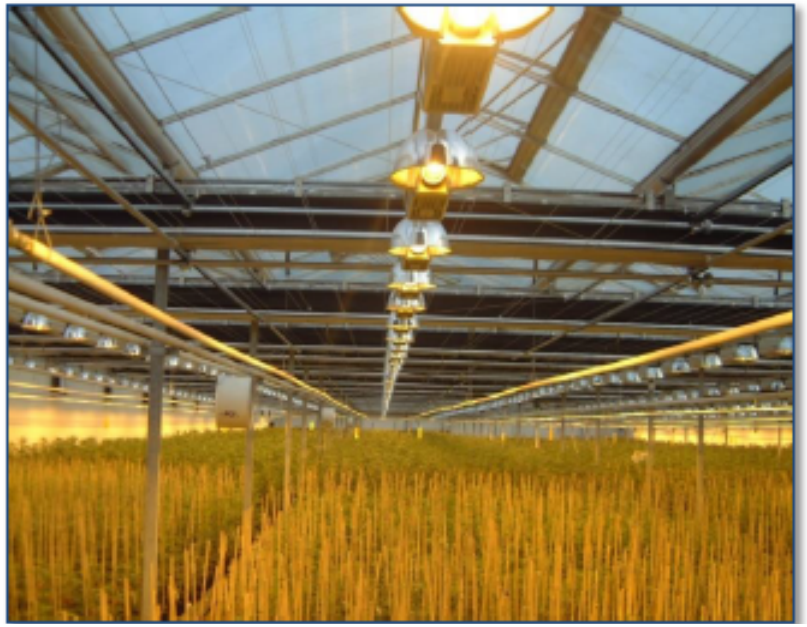
A groundbreaking clinical trial may provide some answers to medical marijuana as a seizure treatment

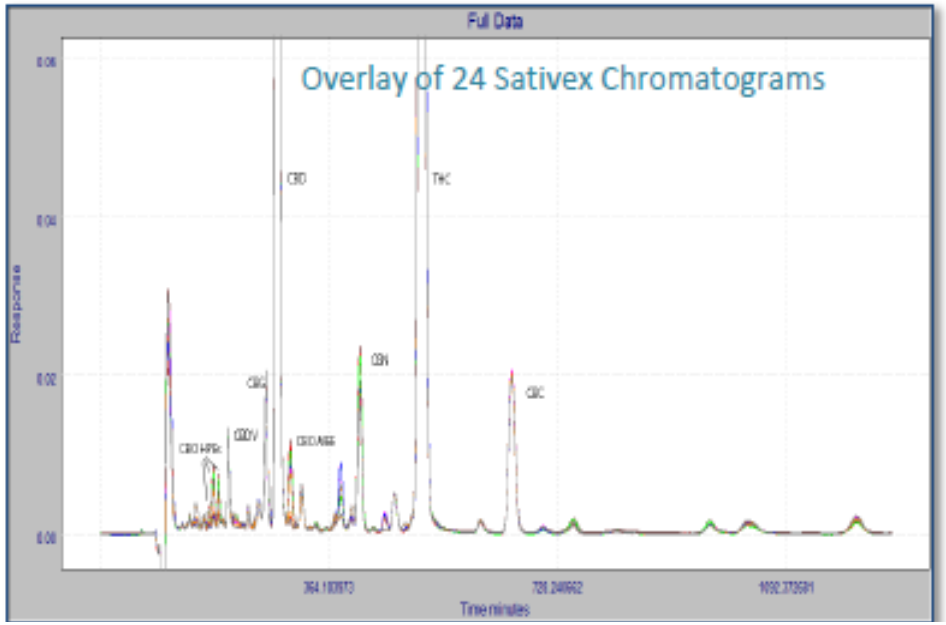
Correction appended, Sept. 5, 2014

For years, some parents have turned to medical marijuana to treat their children's

Cannabinoids: GW Pharma

- GW's novel proprietary plant "chemotypes" target selected cannabinoids
  - CBD, THC, CBC, CBG, CBN, THCV, CBGV, CBDV, THCA, CBDA etc
- In-house formulation, processing, manufacturing and regulatory expertise
- Exclusivity via 46 patent families, know-how, complex formulations
  - Specialized field provides substantial barriers to entry





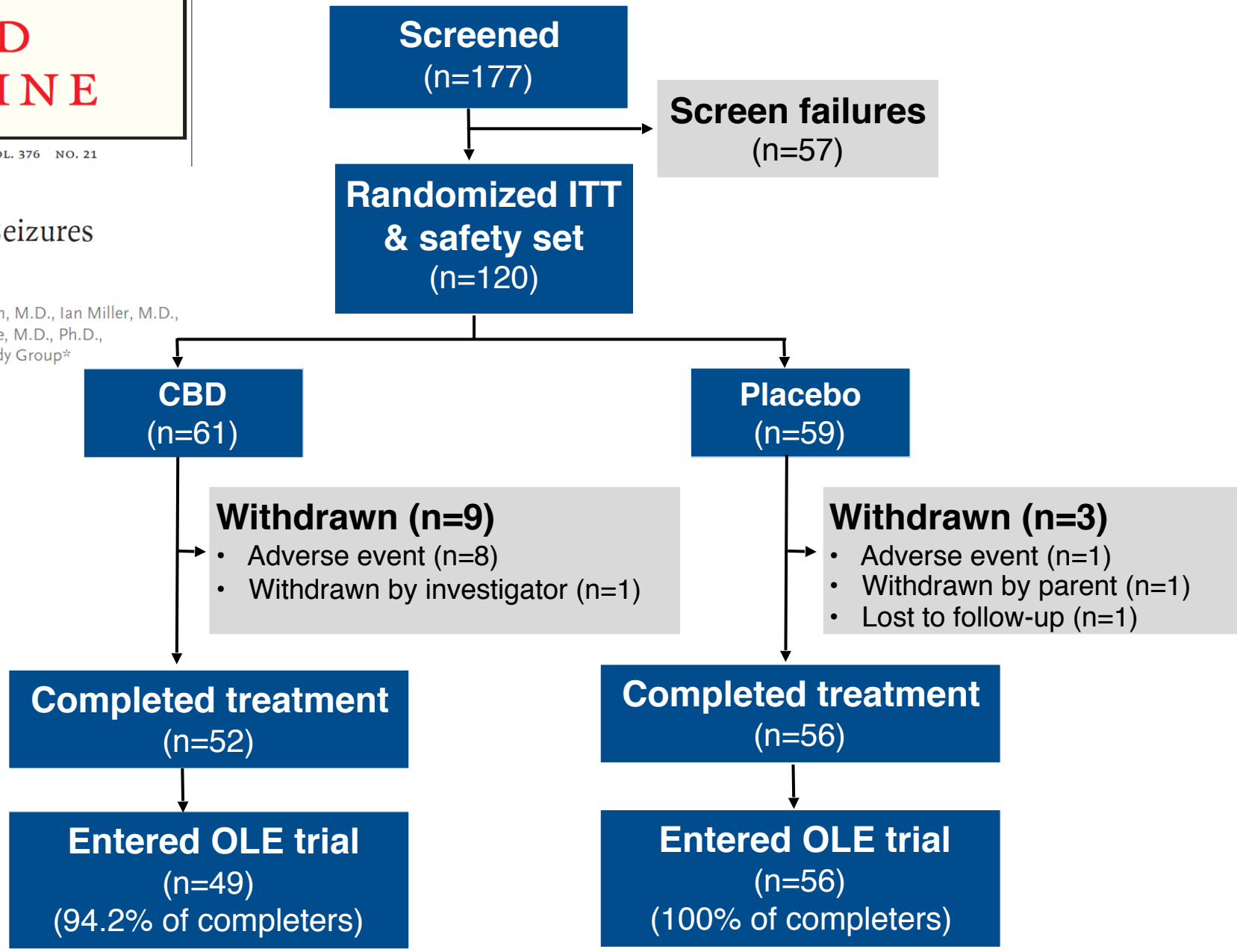
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 25, 2017 VOL. 376 NO. 21

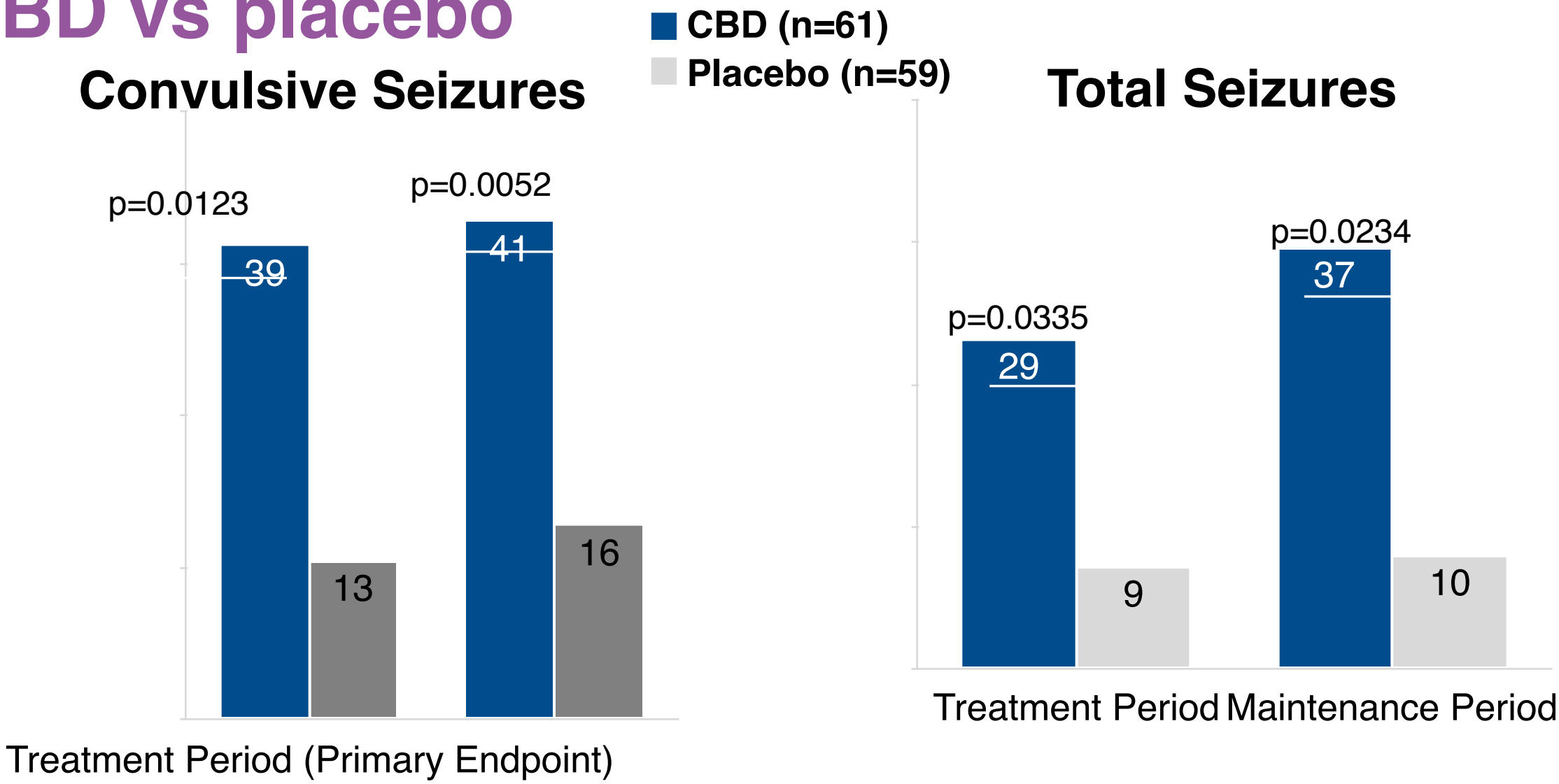
Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabbout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D., and Stephen Wright, M.D., for the Cannabidiol in Dravet Syndrome Study Group*

23 study centers in U.S. and Europe
177 patients screened
120 randomized
85% of CBD and 95% of placebo patients completed



Significantly greater seizure reduction with CBD vs placebo



Key Safety Results

Treatment-Emergent Adverse Events (TEAEs)	CBD (n=61) n (%)	Placebo (n=59) n (%)
TEAEs reported in >10% of patients in either group by preferred term		
Somnolence	22 (36.1)	6 (10.2)
Diarrhea	19 (31.1)	6 (10.2)
Decreased appetite	17 (27.9)	3 (5.1)
Fatigue	12 (19.7)	2 (3.4)
Pyrexia	9 (14.8)	5 (8.5)
Vomiting	9 (14.8)	3 (5.1)
Lethargy	8 (13.1)	3 (5.1)
Upper respiratory tract infection	7 (11.5)	5 (8.5)
Convulsion	7 (11.5)	3 (5.1)

Laboratory Investigations

- Increases in ALT or AST (>3× ULN) occurred in 12 CBD and 1 placebo patient, all of whom were on concomitant valproic acid
- No patients met standard criteria for drug-induced liver injury with concurrent elevated bilirubin >2× ULN
- Three CBD patients withdrew from treatment due to the elevated transaminases
- All elevations resolved

AED interaction; clobazam

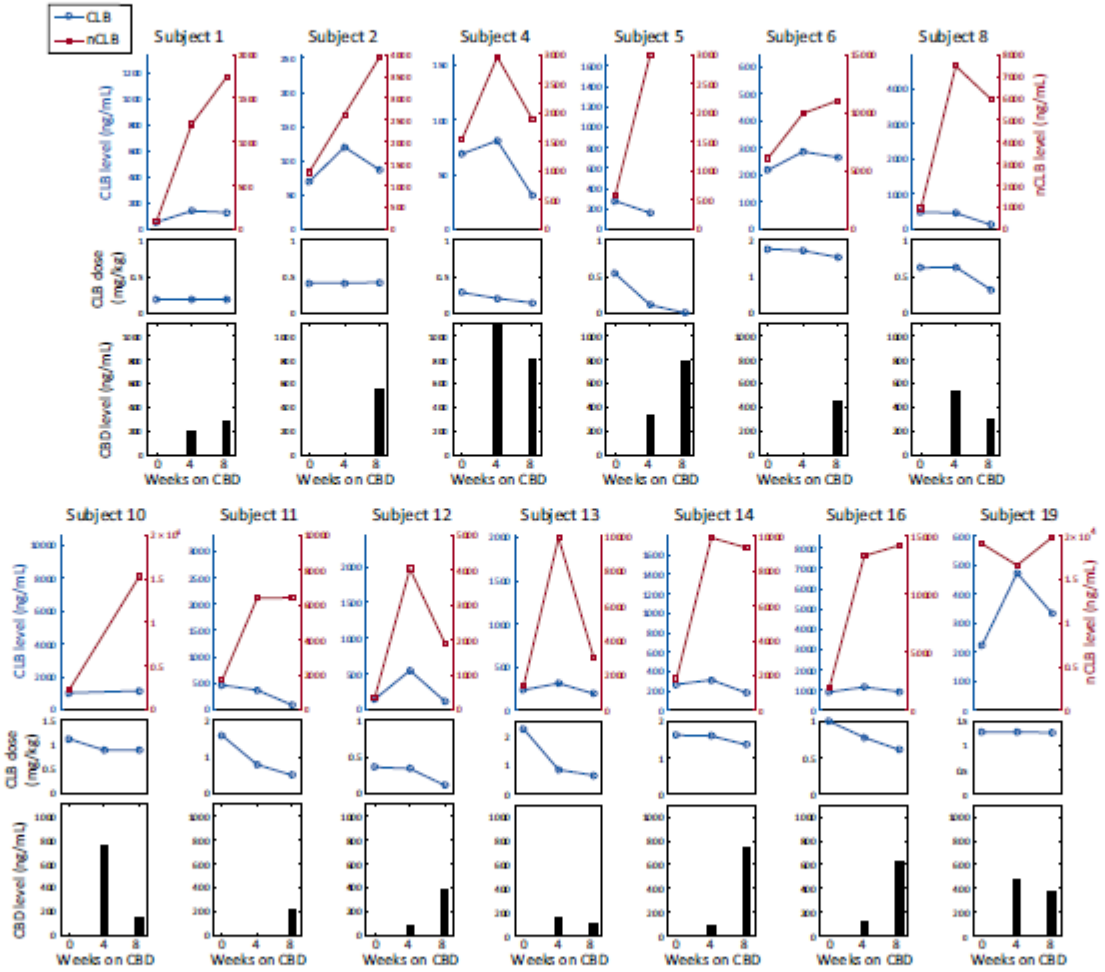
13/25 children CBD 2—25mg/kg/day

Mass General Hospital, Boston

Norclobazam increased in 12/13

Side effects 10/13

- Drowsiness 6
- Ataxia 2
- Irritability 2
- Restless sleep 1
- Urinary retention 1
- Tremor 1
- Loss of appetite 1



Geffrey et al, Epilepsia, 56(8):1246–1251, 2015

ARTICLE OPEN ACCESS CLASS OF EVIDENCE

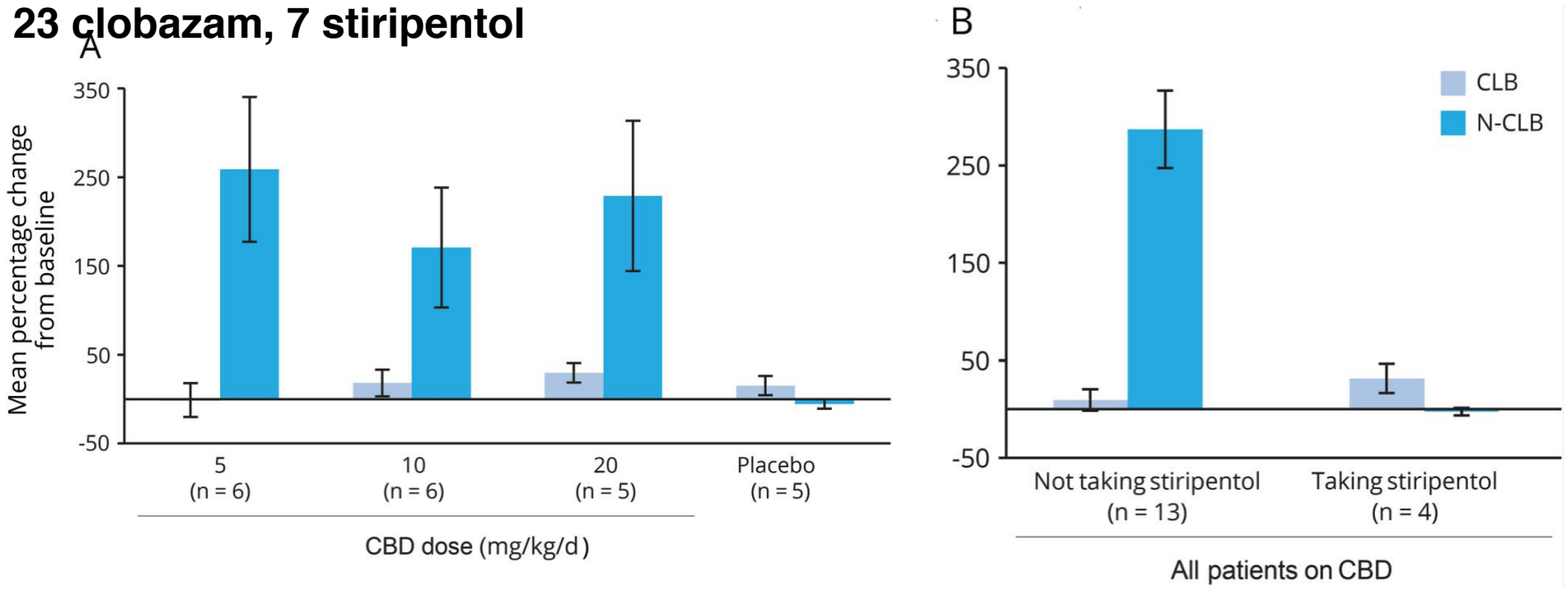
Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome

Neurology 2018;90:e1204-1211

Orrin Devinsky, MD, Anup D. Patel, MD, Elizabeth A. Thiele, MD, Matthew H. Wong, MD, Richard Appleton, MD, Cynthia L. Harden, MD, Sam Greenwood, PhD, Gilmour Morrison, and Kenneth Sommerville, MD, On behalf of the GWPCARE1 Part A Study Group

Correspondence
Dr. Devinsky
Od4@nyu.edu

34 patients, randomised to placebo, 5mg/kg, 10mg/kg, 20mg/kg
23 clobazam, 7 stiripentol



NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Cannabidiol with clobazam for treating seizures associated with Dravet syndrome

1 Recommendations

1.1 Cannabidiol with clobazam is recommended as an option for treating seizures associated with Dravet syndrome in people aged 2 years and older, only if:

- the frequency of convulsive seizures is checked every 6 months and cannabidiol is stopped if the frequency has not fallen by at least 30% compared with the 6 months before starting treatment
- the company provides cannabidiol according to the commercial arrangement (see section 2).

1.2 This recommendation is not intended to affect treatment with cannabidiol, with clobazam, that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place before this

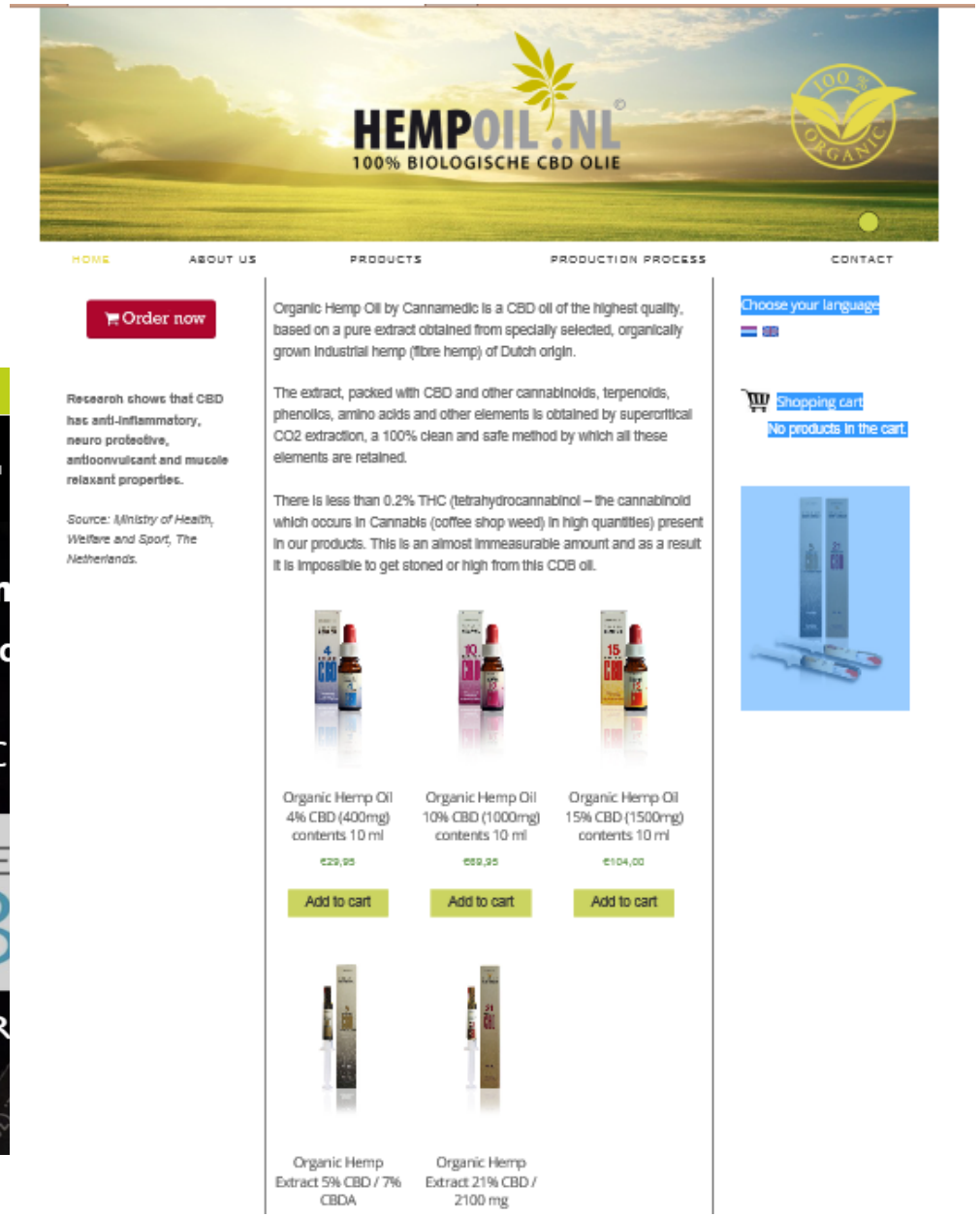
Draft 11th November 2019
Due publication 18th December 2019

First line	**Broad spectrum ASM: Valproate**
Diagnosis clear and continuing seizures **Second line** **(evidence based RCT)**	**Valproate + stiripentol +/- clobazam or add-on Cannabidiol**
Alternatives for second line	**Ketogenic diet** **Clobazam** **Topiramate** **Bromide** **Vagal nerve stimulation**

Cross et al Epilepsia 2019 in press

Hemp oil

<0.3% THC



Not the same!!

Cannabidiol dose and label accuracy in edible medical cannabis products

JAMA June 23/30, 2015 Volume 313, Number 24

August to October 2014; individuals sent to dispensaries in San Francisco, Los Angeles, and Seattle, USA.
Entire package contents were assessed

Table 1. Accuracy of Product Labeling

	Accuracy of Labeled Tetrahydrocannabinol (THC) Content		
	Accurately Labeled[a]	Underlabeled[b]	Overlabeled[c]
Overall (3 Cities)			
Products tested, No. (%) (N = 75)	13 (17)	17 (23)	45 (60)
Type of product, No.			
Baked goods	2	7	13
Beverages	3	2	8
Candy or chocolate	8	8	24
Amount of THC, mg			
Label range	15 to 200	20 to 1000	2 to 325
Actual range	15 to 183	34 to 1236	<1 to 267
Deviation in THC content amount, %[d]			
Mean (SD)	−3 (4)	28 (13)	−47 (29)
Maximum	9	55	−99

Table 2. Observed Cannabinoid Content

	Cannabinoid Content, mg	
Type of Cannabinoid	Median (IQR)[a]	Range
Tetrahydrocannabinol	54 (99)	<1-1236
Tetrahydrocannabinolic acid	2 (15)	<1-173
Cannabidiol	2 (3)	<1-51
Cannabidiolic acid	1 (5)	<1-20
Cannabigerol	3 (3)	<1-43
Cannabinol	2 (2)	<1-20

[a] Presented because observed values were not normally distributed.

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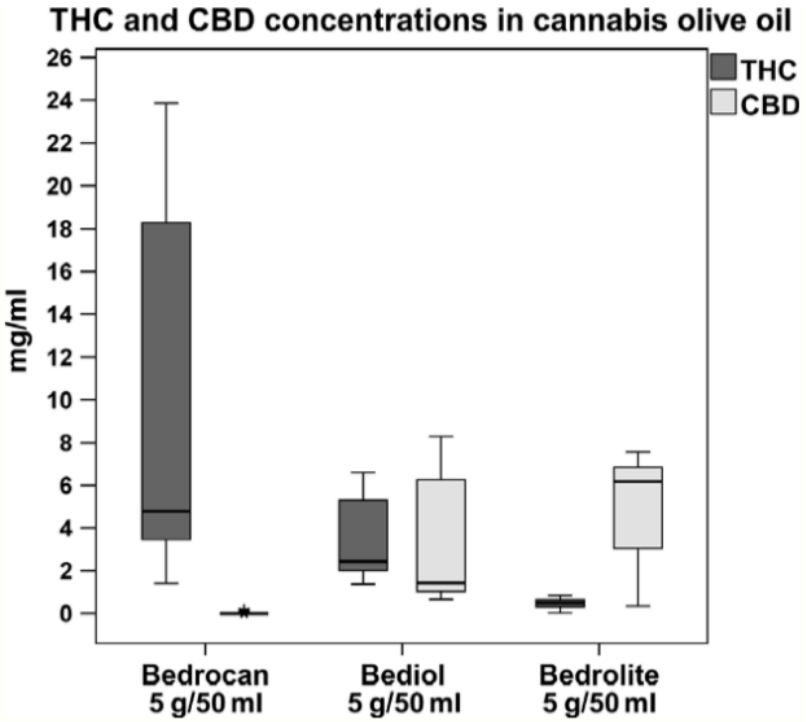
JPP Journal of Pharmacy And Pharmacology
Research Paper

Cannabinoids concentration variability in cannabis olive oil galenic preparations

Chiara Carcieri[a,c]*, Cristina Tomasello[a,b]*, Marco Simiele[a,e], Amedeo De Nicolò[a], Valeria Avataneo[a], Luca Canzoneri[d], Jessica Cusato[a], Giovanni Di Perri[c,e] and Antonio D'Avolio[a,e]

[a]Laboratory of Clinical Pharmacology and Pharmacogenetics, Department of Medical Sciences, University of Turin, Turin, Italy, [b]Hospital Pharmacy, Maria Vittoria Hospital, ASL CITTA' DI TORINO, Turin, Italy, [c]Unit of Infectious Diseases, Department of Medical Sciences, University of Turin, Turin, Italy, [d]Pain Management Center, San Luigi Hospital, Orbassano, Turin, Italy and [e]CoQua Lab s.r.l, Academic Spin-off of University of Turin, Turin, Italy

- poor standardization is currently applied to the gale-nic preparation of cannabis oil extracts,
- evaluation of their interlot variability from 188 different laboratories
- 201 cannabis oil samples from 10 different pharmacies were collected and their main cannabinoids levels quantified by LC-MS system.
- median extraction rates for Bedrocan, Bediol, Bedrolite 5 g/ml were 90% THC/THCA, ND CBD/CBDA;102% THC/THCA, 100% CBD/CBDA; 108% THC/THCA,75% CBD/CBDA, respectively. Statistically significant differences, with a higher THC extraction yield for Bediol than Bedrocan ($P < 0.001$) and higher extraction yield of CBD for Bediol than Bedrolite ($P < 0.001$)



ANNALS of Clinical and Translational Neurology
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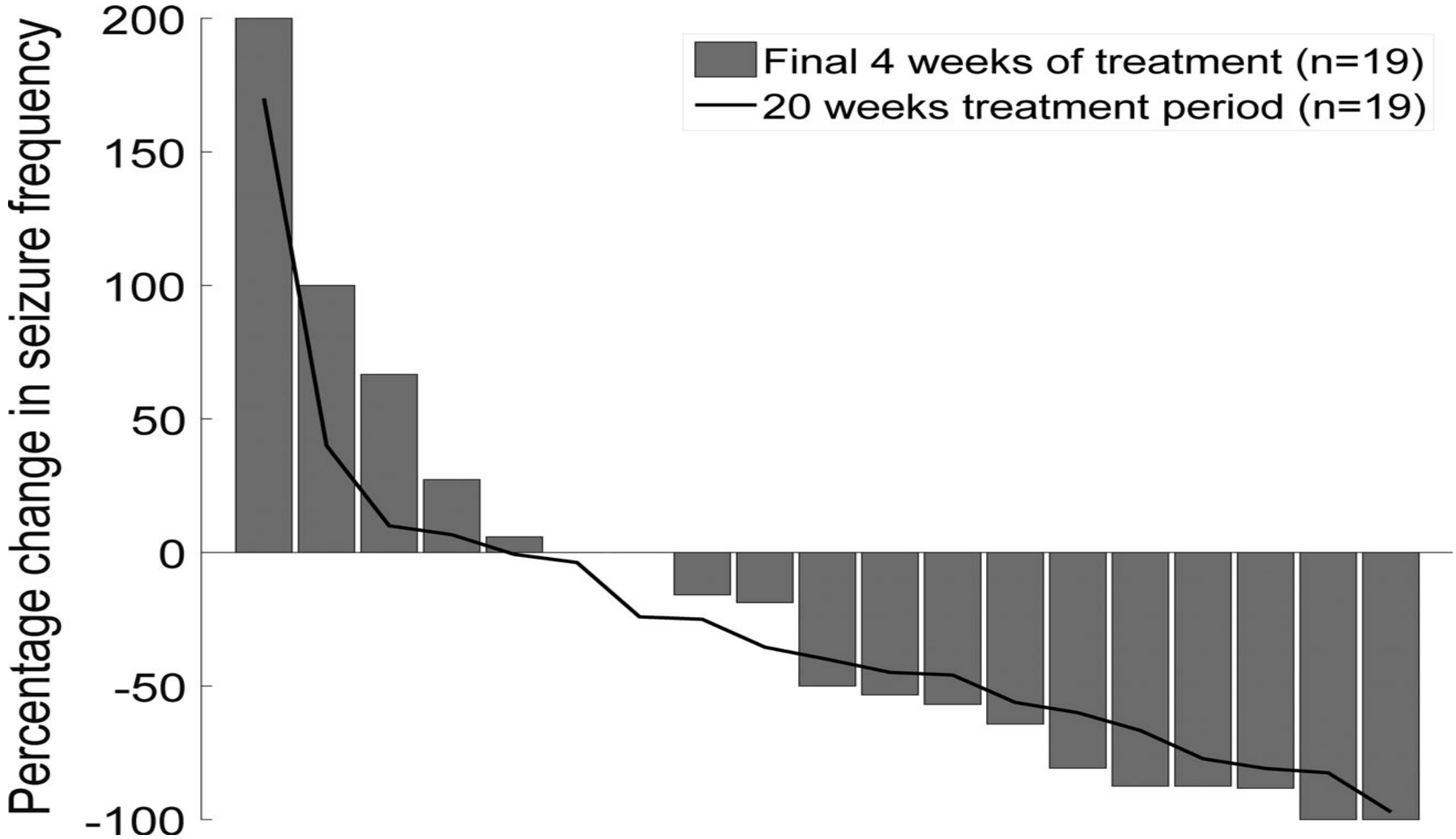
RESEARCH ARTICLE

A prospective open-label trial of a CBD/THC cannabis oil in dravet syndrome

Bláthnaid McCoy[1,2], Laura Wang[3], Maria Zak[1], Sameer Al-Mehmadi[1], Nadia Kabir[1], Kenda Alhadid[1], Kyla McDonald[4], Grace Zhang[4], Rohit Sharma[1], Robyn Whitney[1,2], Katia Sinopoli[4] & O. Carter Snead III[1]

- Open label add on study
  - TIL-TC150 (Tilray) CBD 100mg/ml THC 2mg/ml
- 20 children; 1-16 yrs SCN1A Dravet syndrome
  - 2-16mg/kg/day CBD
- 4 week baseline, 20 week ontervention
  - 60% (12/20) >50% reduction in seizures
  - One SUDEP during intervention period


Percentage change in seizure frequency
200
150
100
50
0
-50
-100
Final 4 weeks of treatment (n=19)
20 weeks treatment period (n=19)

NICE National Institute for Health and Care Excellence

NICE guideline

ucts

cts

Cannabis-based medicinal products

NICE guideline

Published: 11 November 2019

www.nice.org.uk/guidance/ng144

Rationale for research recommendations

The committee discussed the limited evidence and agreed that it did not warrant a practice recommendation. However, they also agreed that they **should not make a recommendation against the use of cannabis-based medicinal products as this would restrict further research in this area** and would prevent people who are currently apparently benefiting from continuing with their treatment. Specialists, people with epilepsy and their carers should continue to make treatment decisions in the best interests of each person with epilepsy, in line with theGMC's guidance for Cannabis-based medicinal products (NG144) doctors. However, people seeking treatment for severe epilepsy should be made aware that currently there is no clear evidence of the safety and effectiveness of cannabis-based medicinal products.

3 CBD for severe treatment-resistant epilepsy

What is the clinical and cost effectiveness of CBD in epileptic disorders in children, young people and adults?

4 THC in combination with CBD for severe treatment-resistant ere treatment-resistant epilepsy

Does the addition of THC to CBD have an effect on seizure frequency, brain structure and neuropsychological performance when compared with both CBD alone and placebo in epileptic disorders in children, young people and adults?

Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy

Craig A. Press, Kelly G. Knupp, Kevin E. Chapman *

Department of Pediatrics and Neurology, Children's Hospital Colorado, University of Colorado, Anschutz Medical Campus, CO, USA

Epilepsy & Behavior 45 (2015) 49–52

- 75 patients enrolled
  - 23% Dravet syndrome
  - 89% Lennox-Gastaut
- 57% reported no improvement in seizure control
- 33% reported a 50% reduction in seizures
- If the family had moved to Colorado for Cannabis the responder rate was 47% but only 22% for those already in Colorado
- Adverse events occurred in 44% of the patients
  - Increased seizures 13%
  - Somnolence, fatigue 12%

A need for RCTs!

Fenfluramine

- **Racemic mixture of two enantiomers: dextrofenfluramine and levofenfluramine**
  - **Introduced to US market 1973 as appetite suppressant**
  - **Concern re cardiac & pulmonary side effects**
- **1986, Aicardi Jean, *New Engl J Med***
  - **Treatment of photosensitive epilepsy with fenfluramine**
- **1996 Boel & Caesar *Neuropediatrics***
  - **11 with self induced seizures, all responders**
  - **5/11 SCN1A mutation positive**
- **2012 Ceulemans et al *Epilepsia***
  - **7/12 with Dravet Syndrome seizure free**

Low-dose fenfluramine significantly reduces seizure frequency in Dravet syndrome: a prospective study of a new cohort of patients

A. Sch

L. Lagae[f] and

European Journal of Neurology 2016

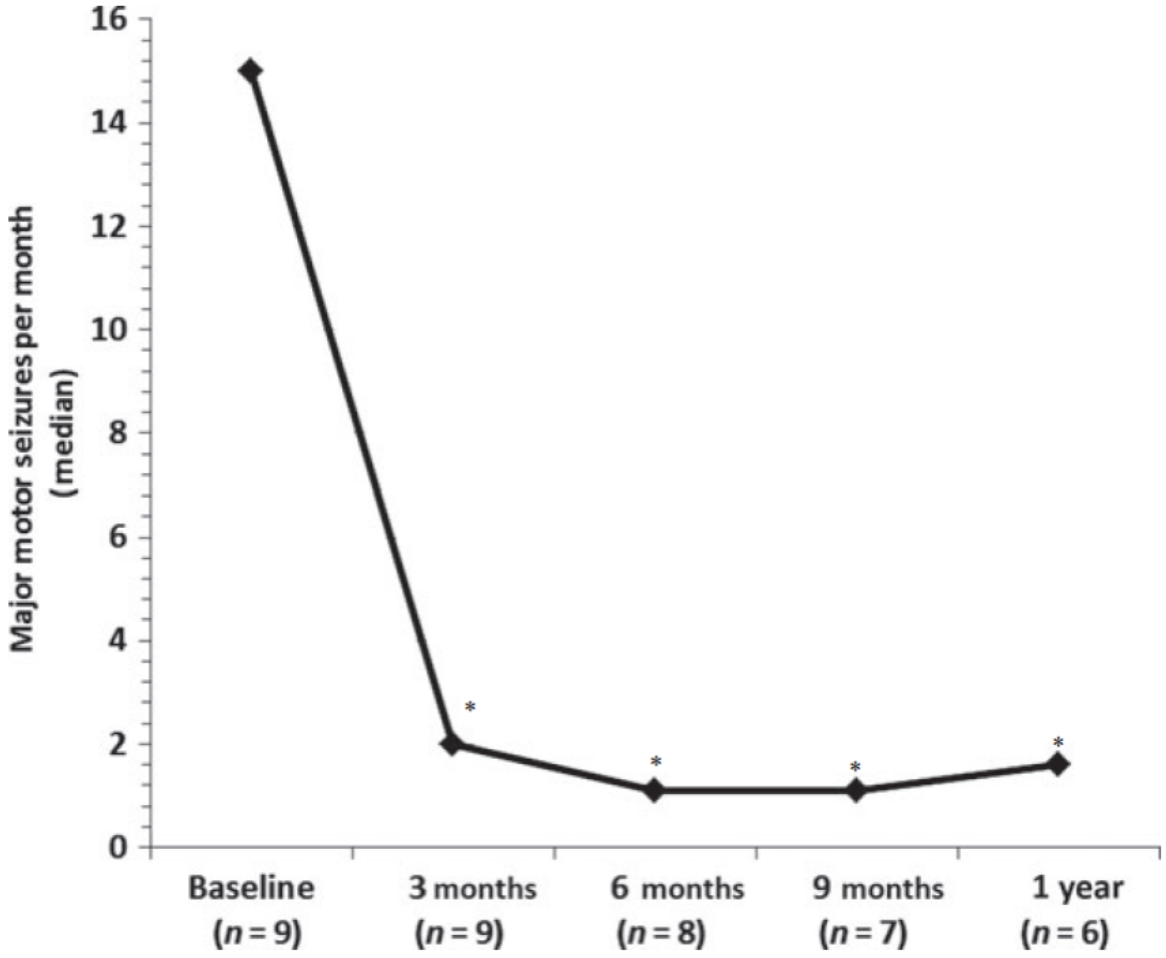


Table 1

Patient		Initial epilepsy treatment regimen at study entry
1	ation (c.4497delT)	VPA, CLB, VNS
2	ation (c.296T>A)	VPA, TPM, CLB
3	ation (c.969T>G)	VPA, TPM
4	.3427-4002 + ?dup)	Bromide, VPA, TPM
5	ation (c.58C>T)	STP, TPM, VPA, ethyl loflazepate
6	ation (IVS22 + 1 G>A)	VPA, TPM, ethyl loflazepate, STP
7	ation (c.2589 + 3A>T)	VPA, LEV, CLB, TPM, VNS
8	tation (c.657-658delAG)	VPA, TPM, ethyl loflazepate
9	ation (c.2875T>C)	VPA, TPM, ethyl loflazepate, VNS

CLB, c piramate; VNS, vagal nerve stimulation; VPA, valproic acid.

Global Phase 3 Program in Dravet Syndrome

ZX008 as adjunctive treatment for seizures in children and young adults with Dravet syndrome

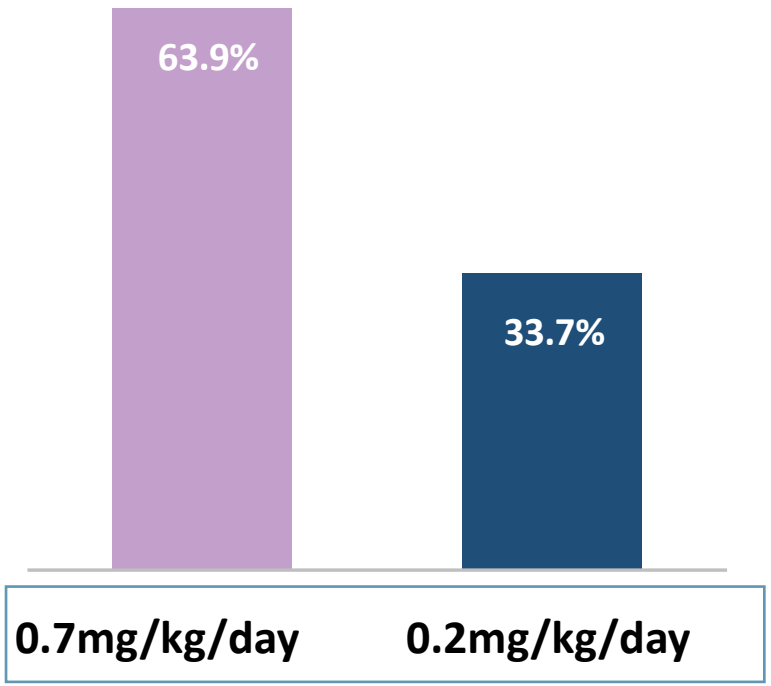
Study 1501 /Study 1502	Study 1504
Double-blind, randomized, placebo-controlled, 12-week treatment **Two active doses (0.2 mg/kg/day, 0.8 mg/kg/day) & placebo**	Double-blind, randomized, placebo-controlled, 12-week treatment **One active dose (0.5 mg/kg/day) & placebo**
U.S. Standard of Care; **Stiripentol excluded**	E.U. Standard of Care; **All patients on stiripentol**
Primary outcome: Change from baseline in frequency of convulsive seizures	Primary outcome: Change from baseline in frequency of convulsive seizures
FDA confirmation of adequate and well-controlled pivotal study design	FDA confirmation of adequate and well-controlled pivotal study design

All patients eligible to enter Study 1503: long-term, open-label, flexible- dose extension

Efficacy of fenfluramine (- stiripentol)

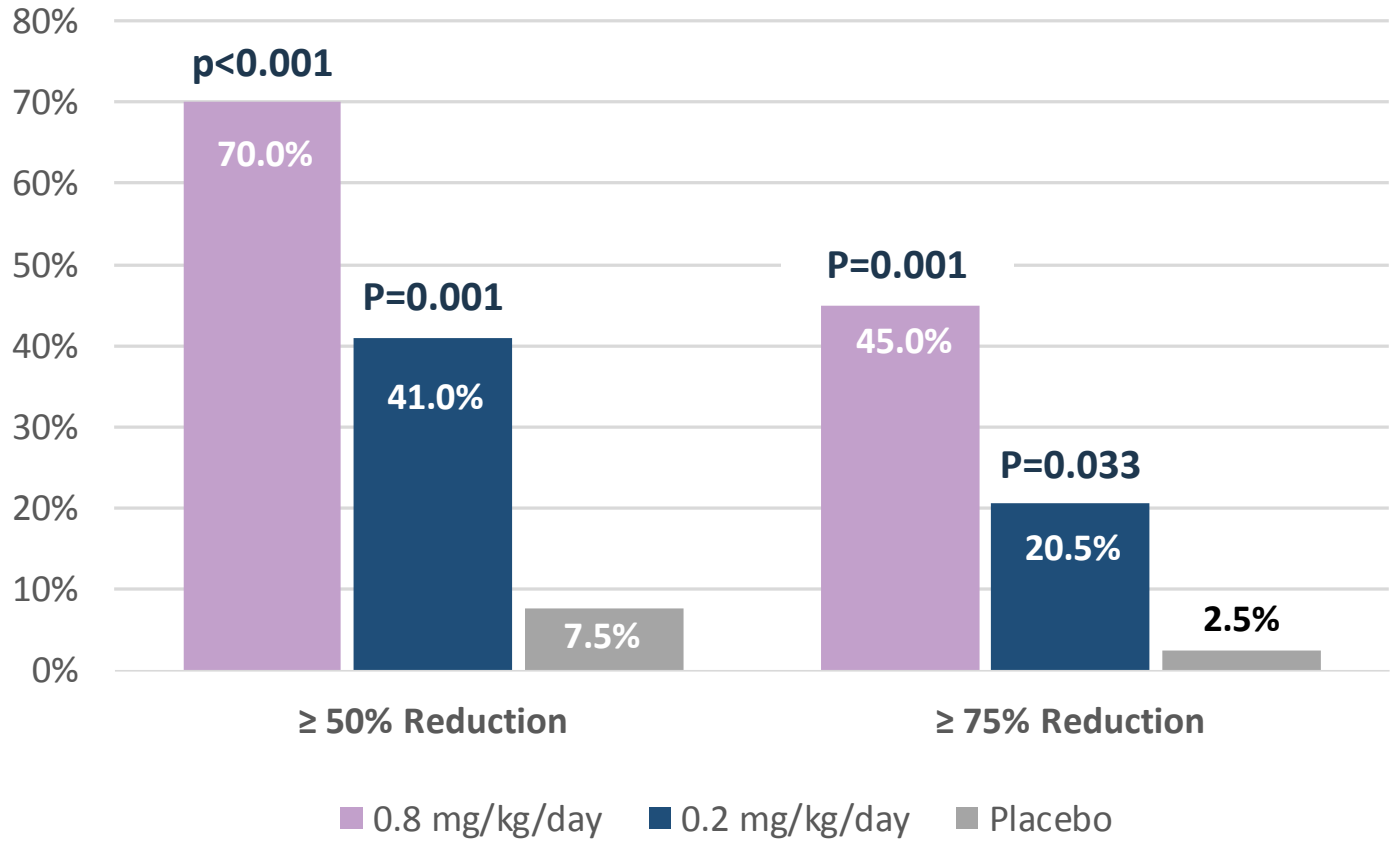
% DIFFERENCE FROM PLACEBO IN REDUCTION IN MEAN MONTHLY CONVULSIVE SEIZURES

(2 WK TITRATION + 12 WK MAINTENANCE PERIOD)



PROPORTION OF PATIENTS WHO ACHIEVED ≥50% AND ≥75% REDUCTION IN MEAN MONTHLY CONVULSIVE SEIZURES

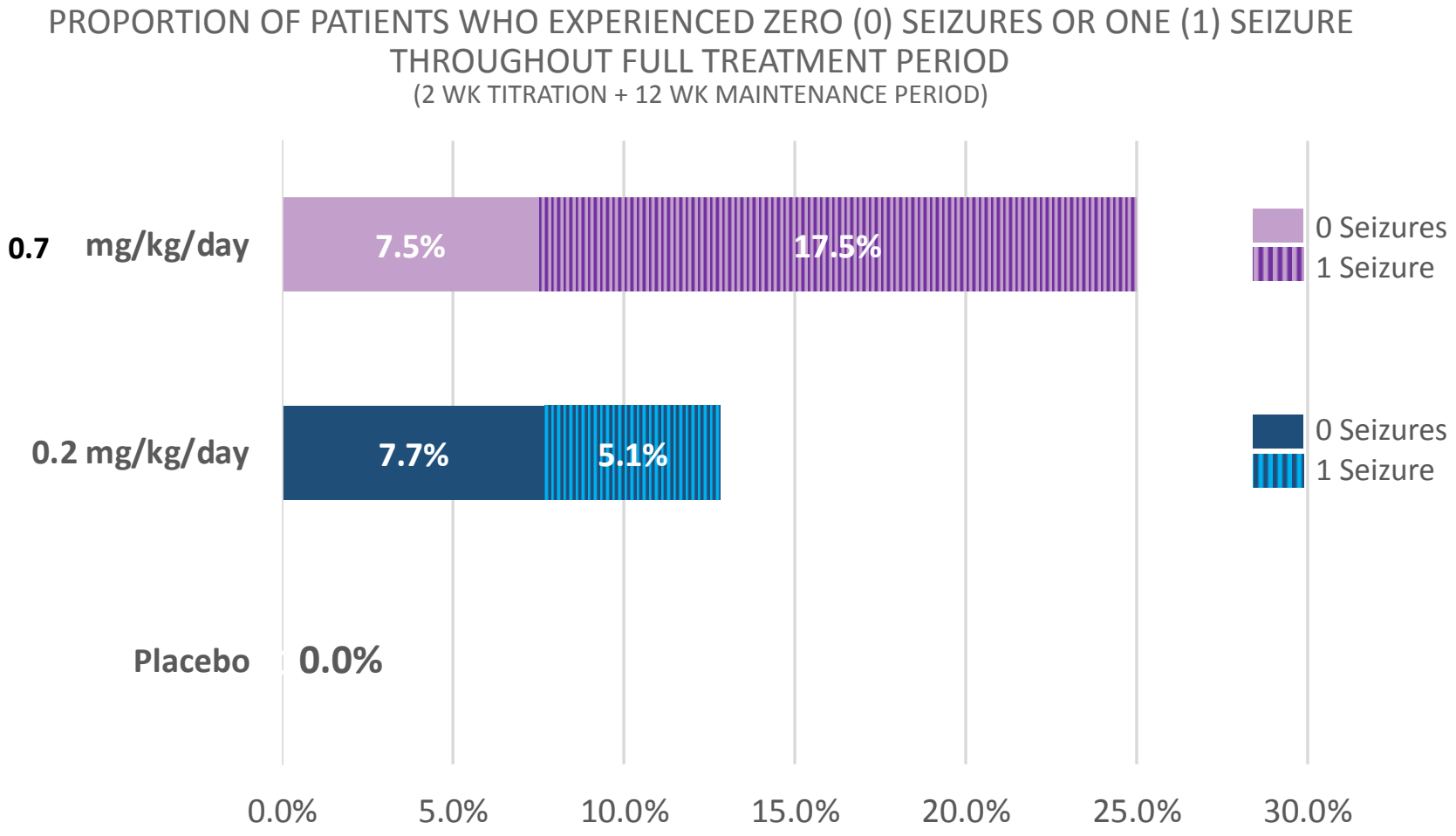
(2 WK TITRATION + 12 WK MAINTENANCE PERIOD)



p-values calculated vs. placebo

Lagae et al Lancet in press

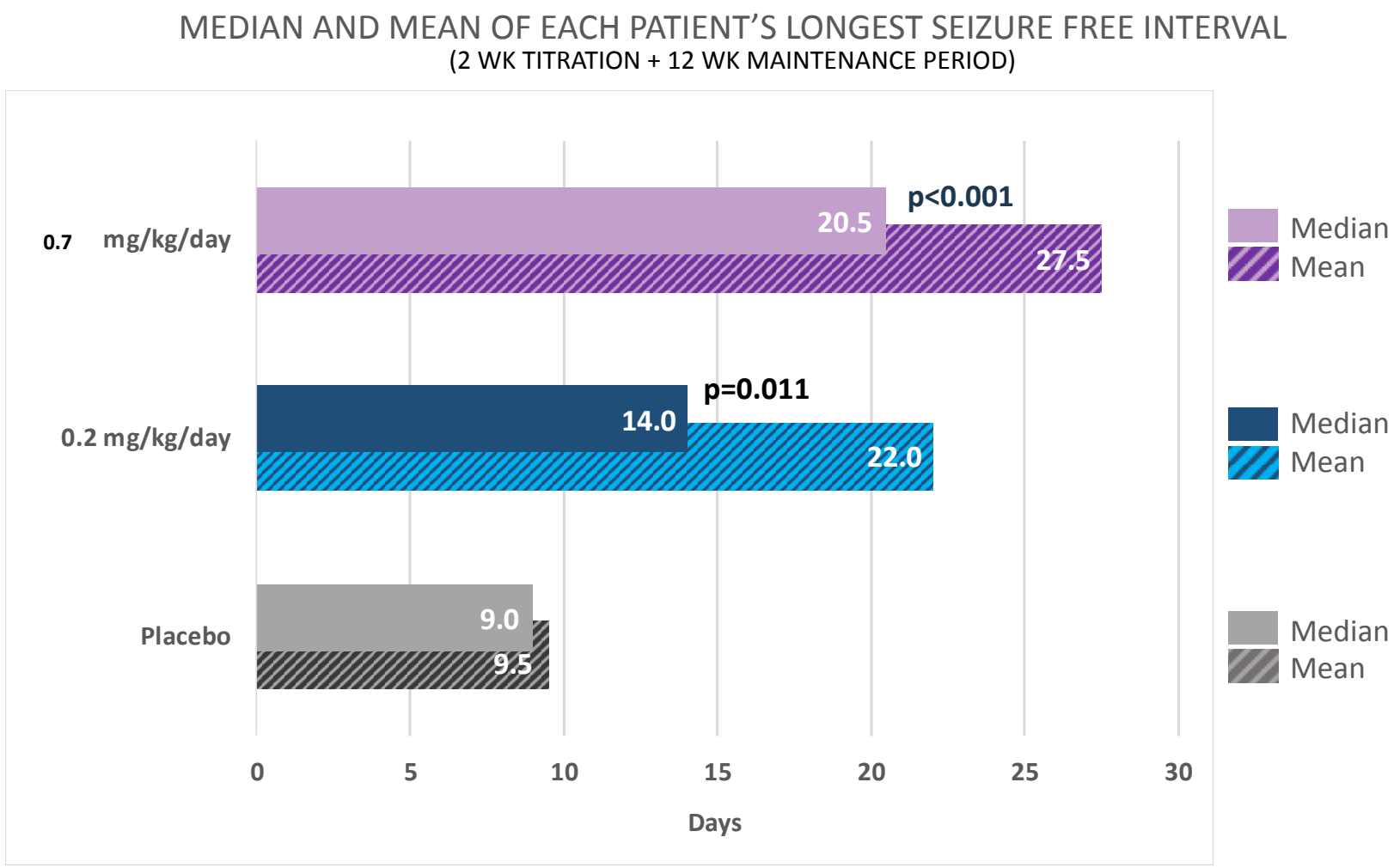
Study 1: Seizure Freedom/Near-Freedom Rates



Note: mean monthly seizure rate at baseline for all patients in Study 1 was 40/month

Lagae et al Lancet in press

Study 1: Longest Seizure Free Interval



p-values are for median values vs. placebo

Lagae et al Lancet in press

Most Common Treatment-Emergent AEs (≥10%)

Study 1

	Placebo	ZX008 0.2 mg/kg	ZX008 0.8 mg/kg
Constipation	0	1 (2.6%)	4 (10.0%)
Decreased appetite	**2 (5.0%)**	**8 (20.5%)**	**15 (37.5%)**
Diarrhea	3 (7.5%)	12 (30.8%)	7 (17.5%)
Echocardiogram abnormal*	5 (12.5%)	7 (17.9%)	9 (22.5%)
Fall	2 (5.0%)	4 (10.3%)	0
Fatigue	1 (2.5%)	4 (10.3%)	4 (10.0%)
Lethargy	2 (5.0%)	4 (10.3%)	7 (17.5%)
Nasopharyngitis	5 (12.5%)	4 (10.3%)	7 (17.5%)
Pyrexia	8 (20.0%)	7 (17.9%)	2 (5.0%)
Seizure	5 (12.5%)	4 (10.3%)	3 (7.5%)
Somnolence	**3 (7.5%)**	**6 (15.4%)**	**4 (10.0%)**
Vomiting	4 (10.0%)	4 (10.3%)	3 (7.5%)
Weight decreased	**0**	**5 (12.8%)**	**2 (5.0%)**

Study 1504 C2

	Placebo	ZX008 0.5 mg/kg
Blood glucose decreased	2 (4.5%)	6 (14.0%)
Bronchitis	2 (4.5%)	5 (11.6%)
Decreased appetite	**5 (11.4%)**	**19 (44.2%)**
Diarrhea	3 (6.8%)	10 (23.3%)
Fatigue	2 (4.5%)	11 (25.6%)
Lethargy	2 (4.5%)	6 (14.0%)
Nasopharyngitis	15 (34.1%)	7 (16.3%)
Pyrexia	4 (9.1%)	2 (5%)
Seizure	7(16%)	5 (11.6%)
Echocardiogram abnormal*	0	4 (9.3%)
Weight decreased	**1 (2.3%)**	**4 (9.3%)**

*** All findings were only of "Trace regurgitation" a normal physiological finding in normal healthy children**

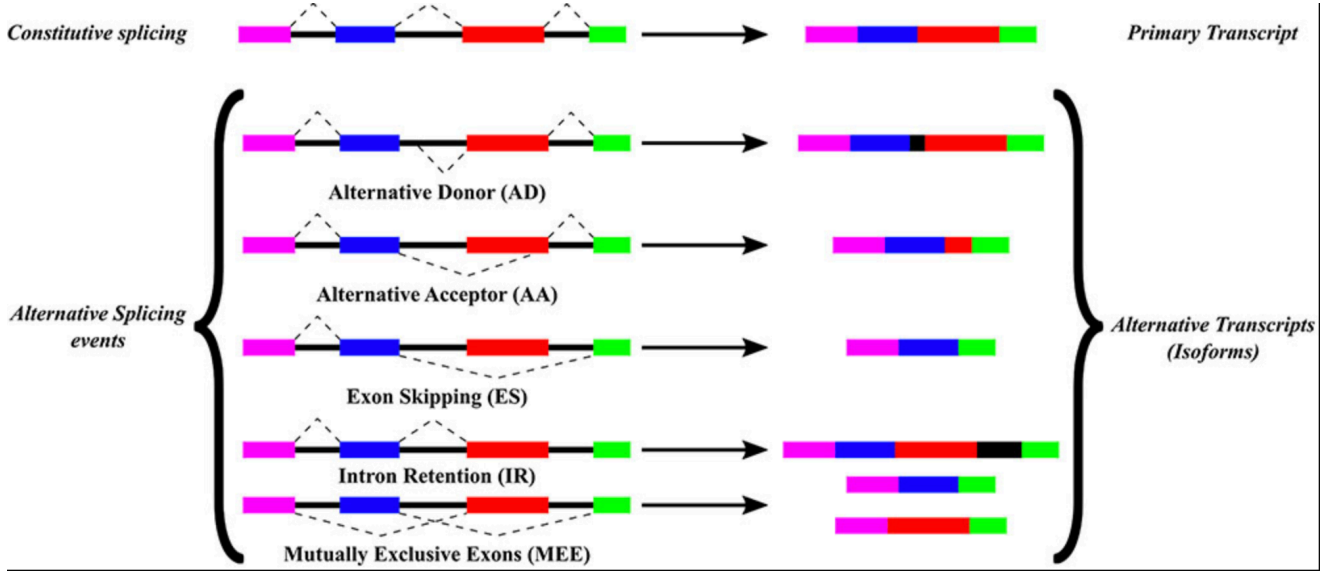
First line	**Broad spectrum ASM: Valproate**
Diagnosis clear and continuing seizures **Second line** **(evidence based RCT)**	**Valproate + stiripentol +/- clobazam or add-on Cannabidiol** ***Or add-on Fenfluramine*** ***(approval conditional)***
Alternatives for second line	**Ketogenic diet** **Clobazam** **Topiramate** **Bromide** **Vagal nerve stimulation**

Cross et al Epilepsia 2019 in press

What about the future?

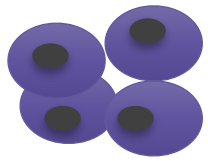
Alternative splicing

- Regulates 90% multiexon genes
- Post-transcriptional control on
  - genome-wide
  - tissue-specific gene expression
- Dynamic changes between
  - brain regions
  - cortical layers
  - development
- 100s of differentially spliced exons preferentially alter key protein domains ± harbor mutations

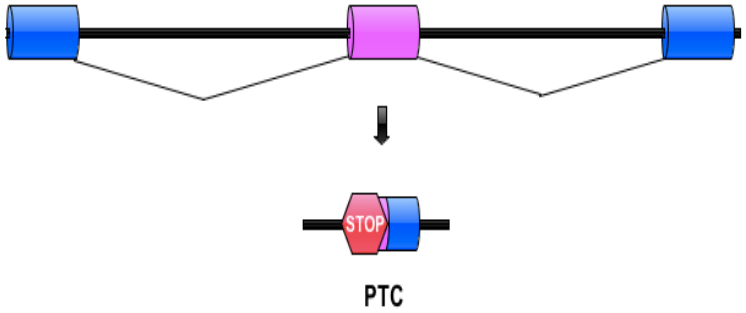


Zhang et al Cell 2016; Iniguez et al 2017

Poison exons

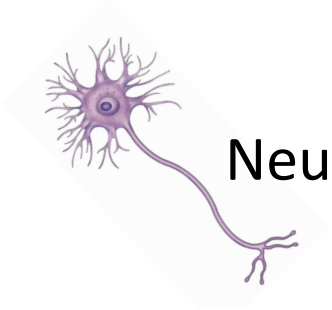


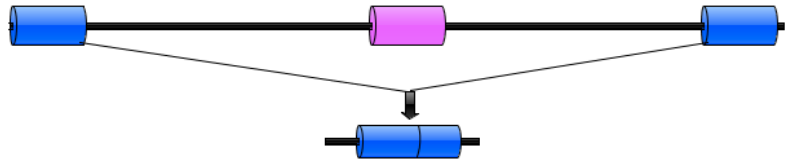
Neural progenitor cells



Thousands of novel truncated transcripts

- Exons small ~27 amino acids
- Surrounding highly conserved ~300 bp regions
- Enriched - chromatin remodelers, sodium channel genes





Full length transcript,
Fully functional protein

Yan et al 2016, Garcia et al 2016, Zhang, 2016

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REPORT

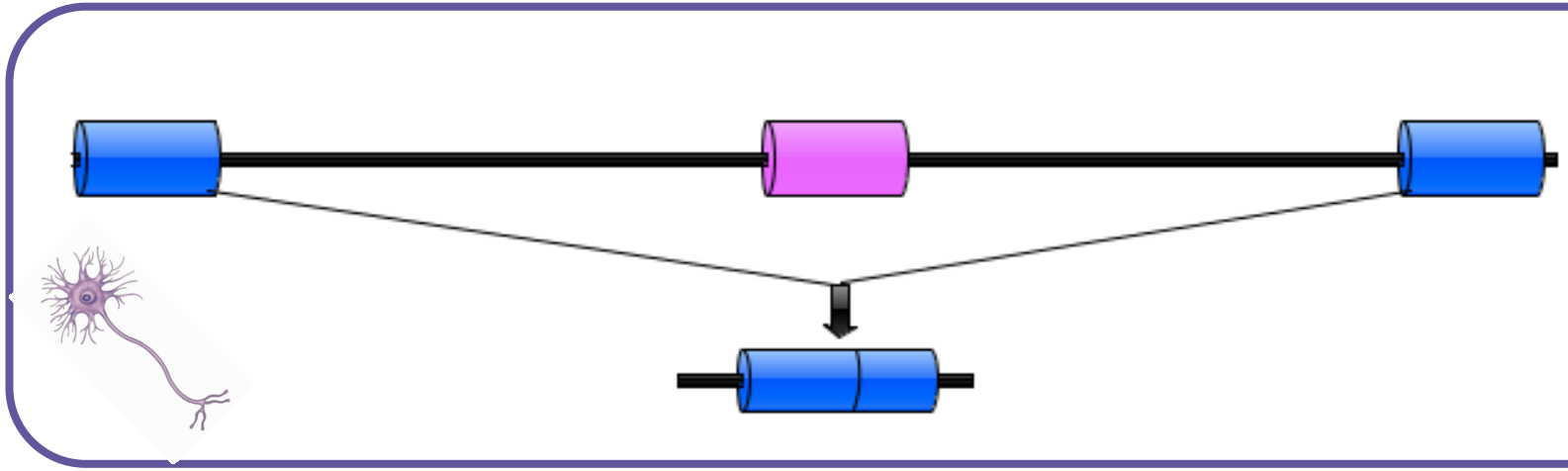
Aberrant Inclusion of a Poison Exon Causes Dravet Syndrome and Related *SCN1A*-Associated Genetic Epilepsies

Gemma L. Carvill,[1,14] Krysta L. Engel,[2,3,14] Aishwarya Ramamurthy,[1] J. Nicholas Cochran,[2] Jolien Roovers,[4,5,6] Hannah Stamberger,[4,5,6] Nicholas Lim,[7] Amy L. Schneider,[8] Georgie Hollingsworth,[8] Dylan H. Holder,[2] Brigid M. Regan,[8] James Lawlor,[2] Lieven Lagae,[9] Berten Ceulemans,[10] E. Martina Bebin,[11] John Nguyen,[7] EuroEPINOMICS Rare Epilepsy Syndrome, Myoclonic-Astatic Epilepsy, and Dravet Working Group, Gregory S. Barsh,[2] Sarah Weckhuysen,[4,5,6] Miriam Meisler,[12] Samuel F. Berkovic,[8] Peter De Jonghe,[4,5,6] Ingrid E. Scheffer,[6,13] Richard M. Myers,[2] Gregory M. Cooper,[2,15,*] and Heather C. Mefford[7,15]

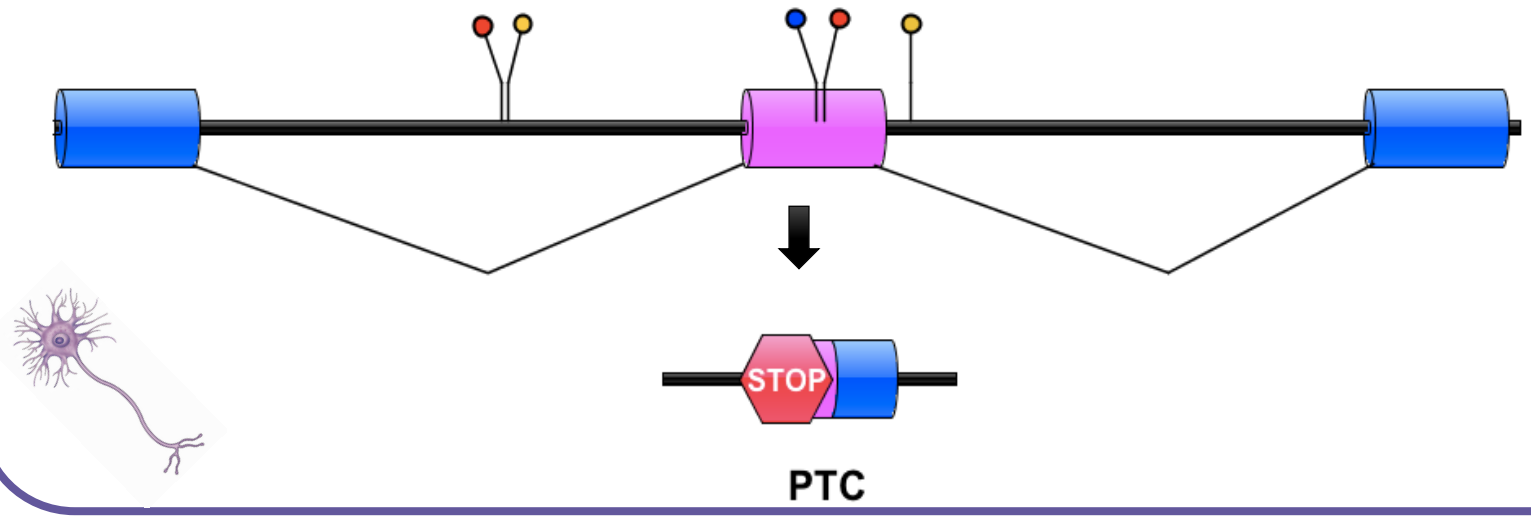
Poison exon

Neuron-specific exons govern transition of neural progenitor cells to neurons

SCN1A variants: putative mechanism



Full length transcript
Fully functional protein in differentiated neurons



Show that the truncated transcript persists in differentiated neurons
→ *SCN1A* haploinsufficiency

Poison Exon

- Intron 20 region under strong selective constraint
- Enriched for rare, deleterious variation in Dravet syndrome
- 20N (nonsense) exon - 64 basepairs

→ aberrant *SCN1A* 20N inclusion

→ reduced full length SCN1A as result of nonsense-mediated decay or truncated SCN1A

→ Mechanism broadly relevant to human disease

→ Neuronal-specific splicing might be co-opted for RNA therapeutics

→ Being trialed in Dravet mouse

Way forward in Dravet syndrome

- **Treatment options widening**
- **Movement of new options into the algorithm – when dependent on approvals**
- **Avoidance of contraindicated medication needs to be considered**
- **Genetic therapies becoming a real possibility**