2nd Line Treatments for Dravet

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Disclosures

- Accepted honoraria from Greenwich Pharmaceuticals, Zogenix, Eisai, Lundbeck, Lineagen.
Overview

Evidence of....
- State of the science of therapies
- Consensus Guidelines
- Pharmacologic therapies
- Non-pharmacologic therapies
- The best is yet to come?
Reading through the literature

PICK A BOX!

systematic review  randomized trial  Cohort Study  Case Series  Mechanistic reasoning
The Literature

- **Level 1** – Systematic review of randomized control trials (RCT) or individual RCT with narrow confidence interval.
- **Level 2** – Systematic review of cohort studies or individual cohort study (including low-quality RCT).
- **Level 3** – Case control studies, outcomes research
- **Level 4** – Case-series
- **Level 5** – Expert opinion

CAVEAT: *LIKELY BEST EVIDENCE IS NOT DEFINITIVE! ‘LOWER LEVEL EVIDENCE MAY PROVIDE STRONGER EVIDENCE THAN ‘HIGHER LEVEL STUDY’ (CASE SERIES WITH DRAMATIC EFFECT VS. SR WITH INCONCLUSIVE RESULTS).*
### Table 1: Second-line medications in Dravet Syndrome

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Level of evidence</th>
<th>AED</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stiripentol</strong></td>
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</tbody>
</table>
| Chiron et al., 2000<sup>19</sup> | Randomized, placebo-controlled                   | 2                 | STP (added to VPA/CLB)                                                | France: 41 patients; 20 placebo, 21 STP  
9 on STP were seizure-free during 2nd month  
Overall 69% reduction in seizures from baseline compared to 7% increase on placebo  
Odds ratio of responding to STP compared to placebo 32 ($\text{CI}_{95\%} = 6.2, 161$) |
| Inoue et al., 2015<sup>15</sup> | Retrospective                                     | 4                 | STP       | 13/24 (54%) achieved a $>$50% reduction in GTCS; 2 were seizure-free                                                                 |
| Wirrell et al., 2013<sup>21</sup> | Retrospective                                     | 4                 | STP       | 82 patients: most children experienced reduction in seizures independent of whether added to VPA or CLB                                |
| Kassai et al., 2008<sup>8</sup> | Meta-analysis of STP                              | 1                 |           | 64 children in 2 randomized control trials; odds ratio of responding to STP relative to placebo was 32 ($\text{CI}_{95\%} = 6.2, 161$), and stiripentol reduced seizures by 70% ($\text{CI}_{95\%} = 93\%, 47\%) |
| **Topiramate**              |                                                   |                   |           |                                                                                                                                        |
| Coppola et al., 2002<sup>10</sup> | Prospective add-on, median follow-up: 12 months   | 3                 | TPM       | 18 patients: 3 seizure-free  
10 had $>$50% reduction                                                                                                                    |
| Nieto-Barrera et al., 2000<sup>11</sup> | Prospective add-on, median follow-up: 10 months  | 3                 | TPM       | 18 patients: 3 (16%) seizure-free  
10 (55%) $>$50% reduction                                                                                                                   |
| Kroll-Seger et al., 2006<sup>23</sup> | Retrospective                                     | 4                 | TPM       | 36 patients: 78% had $>$50% reduction in GTCS  
17% seizure-free for at least 4 months                                                                                                     |
| Dressler et al., 2015<sup>14</sup> | Retrospective                                     | 4                 | TPM       | 35% responders                                                                                                                                 |
| **Bromides and zonisamide** |                                                   |                   |           |                                                                                                                                        |
| Oguni et al., 1994<sup>27</sup> | Add-on, mean follow-up: 19 months                  | 4                 | Bromide   | 22 patients: 8 (36%) $>$75% reduction  
9 (41%) 50-75% reduction in GTCS at 3 months but only 8 responders at 12 months  
Less effective for focal or myoclonic/absence seizures                                                                                     |
| Tanabe et al., 2008<sup>26</sup> | Retrospective questionnaire                       | 4                 | Bromides, ZNS | 42% on bromides and 13.5% on ZNS had no status epilepticus                                                                                   |
| Lotte et al., 2012<sup>25</sup> | Retrospective, review of 32 patients              | 4                 | Bromides  | After 3 months, 81% had $>$50% reduction  
At 12 months, nearly half still had $>$50% reduction in seizure frequency                                                                 |
| **Levetiracetam**           |                                                   |                   |           |                                                                                                                                        |
| Striano et al., 2007<sup>24</sup> | Prospective, add-on, open-label, after 12-week evaluation period | 3                 | LEV       | 28 patients:  
GTCS: 3 seizure-free and 15 with $>$50% reduction  
Myoclonic: 2 seizure-free and 7 $>$50% reduction  
Focal: 3 seizure-free and 3 $>$50% reduction  
Absence: 1 seizure-free and 3 $>$50% reduction                                                                                           |
| **Fenfluramine**            |                                                   |                   |           |                                                                                                                                        |
| Ceulemans et al., 2012<sup>28</sup> | Retrospective, add-on, mean follow-up: 6 years    | 4                 | Fenfluramine | 12 patients: 7 seizure-free for at least 1 year                                                                                         |
Since 2016...

ZX008 (Fenfluramine HCl Oral Solution) in Dravet Syndrome: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial

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

Original Article

Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations From a North American Consensus Panel

Clemizole and modulators of serotonin signalling suppress seizures in Dravet syndrome

A Phase 1b/2a Study to Examine the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-935 as an Adjunctive Therapy in Subjects with Developmental and/or Epileptic Encephalopathies (P5.266)

Behavioral Comorbidities and Drug Treatments in a Zebrafish scn1lab Model of Dravet Syndrome
Current consensus...

First Line
Valproic Acid\textsuperscript{b} or Clobazam\textsuperscript{b}
If first choice not effective, add the other

Second Line
Addition of Stiripentol\textsuperscript{bc}
(used in combination with Valproic Acid and Clobazam)
or Topiramate\textsuperscript{b}
or Ketogenic Diet\textsuperscript{b}
\begin{itemize}
\item < 2 yrs of age: Traditional Ketogenic Diet
\item 2-12 yrs of age: Traditional or Modified Atkins Diet
\item >12 yrs: Modified Atkins Diet
\end{itemize}

Third Line
Addition of an AED:
\begin{itemize}
\item Clonazepam\textsuperscript{b}
\item Levetiracetam\textsuperscript{b}
\item Zonisamide\textsuperscript{b}
\item Ethosuximide\textsuperscript{a} (for atypical absence sz)
\item Phenobarbital\textsuperscript{a}
\end{itemize}
or
Consider Vagus Nerve Stimulator\textsuperscript{a}
with evaluation at a Comprehensive Epilepsy Center
First line therapies – what’s the evidence?

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Responders at 3 months (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KD</td>
<td>60</td>
</tr>
<tr>
<td>VNS</td>
<td>50</td>
</tr>
<tr>
<td>STP+ VPA+ CLB</td>
<td>70</td>
</tr>
<tr>
<td>Bromide</td>
<td>40</td>
</tr>
<tr>
<td>VPA alone</td>
<td>60</td>
</tr>
<tr>
<td>TPM</td>
<td>50</td>
</tr>
<tr>
<td>LEV</td>
<td>30</td>
</tr>
</tbody>
</table>

* VPA, TPM, VNS
**LEV

Retrospective
32 patients

Epilepsy Research (2015) 109, 81–89
Stiripentol

- Open Label (not just Dravet!) 1999
  - Single Blinded placebo controlled arm (n=88): 49% responders, 10% seizure free, 50% median reduction
  - Open Label (n=91): 68% responders, 19% seizure free; 74.5% median reduction
- Dravet, Double Blinded, Placebo, RCT (2000)
  - N=41; 71% responders
  - Valproic acid + clobazam – blinded 2 months, open for 1 month.
  - 71% responders, 69% mean reduction during blinded phase; 43% seizure free.
- Side effects: sleepiness, decreased appetite, ataxia.
Ketogenic diet and Dravet

- Nabbout, et al 2011 – prospective trial of KD+STP+VPA+CLB (+/- TPM and LEV); 15 subjects; 10/15 were 50% responders; 1 seizure free

- Caraballo et al 2011 – retrospective; 24 subjects; 16 (66.5%) remained on diet; 75% had a >75% decrease in seizures.

- Side effects: hyperlipidemia, renal stones, constipation, nausea/vomiting.
Topiramate

- Coppola et. Al (2002) – prospective, open label; 18 subjects; 10 subjects with 50% decrease, 3 subjects with 100% fewer seizures.
- Side effects: cognitive slowing, decreased appetite, acidosis, renal stones, hyperthermia
What’s missing from the 2\textsuperscript{nd} line therapies list?
1857: Bromide approved as anti-convulsant

Possibly more effective for generalized tonic-clonic seizures; 37-77% subjects with >50% seizure reduction, all retrospective (1994-2012).

Side effects: rash, sleepiness, decreased appetite.
Previous strategies:
• Random phenotypic screening
• Structural variation of known AEDs
• Rational, target-based strategies
• Placebo-controlled
• Adjunctive (US) and Non-inferiority (EU; monotherapy)

Mechanisms of AEDs

Modulate GABA potentiation and inhibition of glutamate receptors.

Limitations of previous strategies

- Acute seizure models (MES/PTZ) do not “mirror” epilepsy and do not differentiate against drug-resistant seizures.
- Broad-spectrum drugs not more efficacious than narrow-spectrum drugs (i.e. VPA vs. CBZ).
- Broad-spectrum may not be suitable for different etiologies in difficult to control epilepsy.
- High placebo response rates (less so in MRE).
- Heterogeneity of epilepsy

Molecular pathway advances

Franz D, Capal J, Orphanet Journal of Rare Diseases 2017

Noebels J, Nature Neuroscience 2015

http://epilepsygenetics.net/2014/12/10/beyond-the-ion-channel-and-back/
Unmet needs of drug development

- Treatments of pharmacoresistant epilepsy
- Co-morbidities
- Epilepsy prevention

From the bench…

- Monogenetic etiology + animal model allows for comparison amongst existing compounds.
- Novel targets to modify disease development or progression.
Since 2016...

ZX008 (Fenfluramine HCl Oral Solution) in Dravet Syndrome: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial

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Behavioral Comorbidities and Drug Treatments in a Zebrafish scn1lab Model of Dravet Syndrome
Randomized, placebo-controlled

1:1 placebo and cannabidiol 14 week treatment period.

Seizures tested: tonic, clonic, tonic-clonic, or atonic (convulsive seizures).

Quality of life scales:
- Caregiver global impression of change
- Epworth sleepiness scale
- Quality of Life in Childhood Epilepsy (QOLE)
- Vineland Adaptive Behavioral scales
Seizure-free = 3/60 subjects in the treatment group

Results – Devinsky, et. Al 2017

are shown in Table 3. The end point of a reduction in convulsive-seizure frequency by 50% or more during the treatment period occurred in 43% of the patients in the cannabidiol group and in 27% of the patients in the placebo group (odds ratio, 2.00; 95% CI, 0.93 to 4.30; P = 0.08).

Table 2. Primary Efficacy End Point of Percentage Change in Convulsive-Seizure Frequency in Each Trial Group.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cannabidiol</th>
<th>Placebo</th>
<th>Adjusted Median Difference (95% CI)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of convulsive seizures per mo — median (range)</td>
<td></td>
<td></td>
<td>percentage points</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12.4 (3.9 to 1717)</td>
<td>14.9 (3.7 to 718)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment period</td>
<td>5.9 (0.0 to 2159)</td>
<td>14.1 (0.9 to 709)</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Percentage change in seizure frequency — median (range)</td>
<td>-38.9 (-100 to 337)</td>
<td>-13.3 (-91.5 to 230)</td>
<td>-22.8 (-41.1 to -5.4)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 3. Summary of Secondary End-Point Results during the Treatment Period (Intention-to-Treat Analysis Set).

<table>
<thead>
<tr>
<th>End Point</th>
<th>Cannabidiol vs. Placebo</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change from baseline in other variables†††</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep-disruption score</td>
<td>-0.4 (-1.5 to 0.7)</td>
<td>0.45</td>
</tr>
<tr>
<td>Epworth Sleepiness Scale score</td>
<td>1.5 (-0.2 to 3.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>Quality of Life in Childhood Epilepsy score</td>
<td>1.5 (-3.8 to 6.8)</td>
<td>0.58</td>
</tr>
<tr>
<td>Vineland-II score</td>
<td>-2.6 (-5.8 to 1.6)</td>
<td>0.21</td>
</tr>
<tr>
<td>Inpatient hospitalizations due to epilepsy</td>
<td>0.0 (0.0 to 0.1)</td>
<td>0.54</td>
</tr>
</tbody>
</table>
Side effects

Cannabidiol interactions

- Increase in levels of:
  - Topiramate
  - Rufinamide
  - N-desmethylclobazam
  - Adults – increase in Zonisamide and eslicarbazepine
  - Valproate and LFTs

Devinsky, et al. 2017
Gaston, et al. 2017
Fenfluramine hydrochloride – AES 2017

- Randomized, placebo-controlled
- 1:1:1 placebo and low and higher dose fenfluramine 14 week treatment period.
- Seizure frequency
- Echo (screen/treatment/post-treatment)
Fenfluramine hydrochloride – AES 2017

Figure 3. Percent reduction in mean monthly convulsive seizures for the ZX008 0.8 and 0.2 mg/kg/day groups compared with placebo group reduction during combined titration and maintenance periods.

- **Primary Endpoint**:
  - 0.8 mg/kg/day: 63.9% reduction with p=0.001
  - 0.2 mg/kg/day: 33.7% reduction with p=0.019

Figure 4. Median percent reduction from baseline in convulsive seizures per 28 days during combined titration and maintenance periods.

- 0.8 mg/kg/day: 72.4% reduction with p<0.001
- 0.2 mg/kg/day: 37.6% reduction with p=0.185
- Placebo: 17.4% reduction

Figure 7. Percentage of subjects who experienced seizure freedom or seizure during the combined titration and maintenance periods.

- ZX008 0.8 mg/kg/day: 17.5% seizure-free, 5.1% with 1 seizure
- ZX008 0.2 mg/kg/day: 7.5% seizure-free, 7.7% with 1 seizure
- Placebo: 7.5% seizure-free, 7.7% with 1 seizure

Seizure freedom was a prespecified secondary endpoint. Evaluation of 0 or 1 seizure was completed.
Fenfluramine hydrochloride – AES 2017

Cardiovascular Safety

- No valvulopathy
- Trace mitral regurgitation/Aortic Regurgitation in placebo/0.2/0.8: 12.5%, 17.9%, 22.5%
- Pulmonary hypertension – none
Clemizole and modulators of serotonin signalling suppress seizures in Dravet syndrome

Zebrafish models identifies several compounds:
- Clemizole
- Trazodone
- Lorcaserin (prescribed to Dravet patients)

and generalized tonic-clonic (GTC) seizures, side effects and concurrent AEDs.

The clinical characteristics of Dravet syndrome children treated with Belviq® are summarized in Table 1. There were no deaths among the five Belviq®-treated patients, and Belviq® was well tolerated without serious adverse events causing cessation of therapy. During off-label Belviq® treatment, one patient was initially seizure-free for 3 weeks, one patient was seizure-free for 2 weeks, and a third patient had 1–2 seizure-free days per week. All five patients exhibited a reduction in the total number of seizures. Generalized tonic-clonic seizures were significantly reduced in Patients 1, 2 and 3. Indeed, Patient 2 experienced a 90% reduction in generalized tonic-clonic seizures with no need for rescue medications. Two patients remain on Belviq® with no increase in seizure frequency and, as expected, the most common side effect noted was a decreased appetite. One patient restarted medication a second time with interim improvement for a short period of time and then tapered off.
In process of study…

TAK935

- Inhibitor of Cholesterol 24 hydroxylase
- Phase 1a/2b adult epileptic encephalopathy study ongoing
- Pediatric Dravet/LGS study starting
- Efficacy results not released; safety data appears to be well-tolerated.

Asgharnejad, et. Al AAN 2018
Behavioral Comorbidities and Drug Treatments in a Zebrafish *scn1lab* Model of Dravet Syndrome

<table>
<thead>
<tr>
<th>Zebrafish Behavior</th>
<th>Human Behavior</th>
<th>Valproate</th>
<th>Clemizole/Diazepam</th>
<th>Trazodone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night locomotor activity</td>
<td>Sleep disturbance</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Time spent in open field</td>
<td>Anxiety</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Is it time for a new consensus?

- Approved or hopefully soon-to-be-approved therapies offer higher level data in which older 1\textsuperscript{st} line therapies in addition to 2\textsuperscript{nd} line therapies may be replaced.
- Looking forward to more published accounts of pivotal studies.
- How well do these medications work without valproic acid or clobazam.
- Open-label extensions important to see lasting effect of therapies.
- Therapies to address co-morbidities
Questions?

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