New AEDs in Pediatric Epilepsy

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Timeline: ASD approvals by FDA since 1990

Number of AEDs

Year


Ezogabine (Potiga™)
Eslicarbazepine (Zebinix™)
Perampanel (Fycompa™)
Clobazam (Onfi™)
Zonisamide (Zonegran™)
Lamotrigine (Lamictal™)
Topiramate (Topamax™)
Pregabalin (Lyrica™)
Oxcarbazepine (Trileptal™)
Levetiracetam (Keppra™)
Vigabatrin (Sabril™)
Rufinamide (Banzel™)
Brivaracetam (Rikelta™)
Lacosamide (Vimpat™)

Not approved

http://www.accessdata.fda.gov
Gabapentin

- **Efficacy**
  - Partial with/without generalization, refractory/benign
  - Adjunctive, monotherapy

- **Adverse events**
  - Neurotoxicity, hyperactivity (DD)

- **Advantages:**
  - Fast titration, well tolerated
  - Linear pK, no interactions

- **Disadvantages:**
  - Perception

JM Pellock, 2003
## Significant Reduction in Seizure Frequency with Pregabalin

<table>
<thead>
<tr>
<th>Pregabalin Dose (mg)</th>
<th>Median % Change from Baseline</th>
<th>French et al.</th>
<th>Arroyo et al.</th>
<th>Beydoun et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 BID</td>
<td>35</td>
<td>*</td>
<td></td>
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<tr>
<td>150 BID</td>
<td>37</td>
<td>*</td>
<td></td>
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<tr>
<td>300 BID</td>
<td>51</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBO TID</td>
<td>-1</td>
<td></td>
<td>17</td>
<td>* P≤0.01 vs placebo</td>
</tr>
<tr>
<td>50 TID</td>
<td>*</td>
<td></td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>200 TID</td>
<td>*</td>
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<td>48</td>
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</table>

PBO PBO PBO

*P≤0.01 vs placebo

The most common adverse events occurring during all controlled clinical trials for patients taking pregabalin vs those taking a placebo were dizziness, somnolence, dry mouth, edema, blurred vision, weight gain, and thinking abnormal (primarily difficulty with concentration/attention).

Pregabalin Dosing Instructions

- If needed, may increase to 300 mg/day within 1 wk
- Some postherpetic neuralgia and partial-onset seizure patients may benefit from up to 600 mg/day based on individual response and tolerability
- Dosage adjustment may be necessary in patients with renal insufficiency, based on creatinine clearance
- Pregabalin may be taken with or without food
- Adverse events may increase with dose

Lamotrigine

- Efficacy
  - Partial, generalized, Lennox-Gastaut syndrome

- Adverse events
  - Neurotoxicity, rash, insomnia
  - Severe rash 1:100 - 1:200

- Advantages: children awaken, broad spectrum

- Disadvantages: slow titration, dose AED dependent, life-threatening rash/hypersensitivity
Lamotrigine: Adjunctive Therapy for Partial Seizures in Children Aged 2-16 Years

% of Patients with ≥50% Seizure Reduction (All Partial Seizures)

- Partial Seizure Frequency:
  - 1-18 Weeks: 42%
  - 7-18 Weeks: 45%

- Secondary Generalized Seizure Frequency:
  - 1-18 Weeks: 25%
  - 7-18 Weeks: 28%

LTG vs Placebo:
- p<0.001
- p=0.004
- p=0.003
- p=0.001

Duchowny M, Pellock JM, et al., Neurology 1999
Lamotrigine Rash

- Potentially severe, life threatening
  - Adults: 1:1,000
  - Children: 1:100 - 1:200
- Overall, rash increased by VPA; rapid escalation
- Differentiate benign (10%) from serious cases
- Recommend discontinuing LTG if rash occurs
- Risk of discontinuation in patients with rash Hx:
  - Overall 2.8x
  - AED rash 3.8x
AED Rash and Pharmacogenetics

- SJS/TEN 2 to 3 x greater prevalence in Han Chinese
- With CBZ 25-33% Asian vs. 5-6% Europeans
- HLA-B 1502 allele in 59/60 Han Chinese in Taiwan vs. 6/144 controls and 1/31 maculopapular or HSS
- SJS/TEN susceptibility locus maps tightly and presumptively activates CD8 T lymphocyte

Questions remain:
- Screen all Han Chinese? LTG? Other populations with same/other alleles?

Miller, Ep Curr, 2008
LTG Aseptic Meningitis

- FDA Revised label 2010
- 40 cases reported in 5 year period (46 million Rx)
- Symptoms: headache, fever, chills, nausea, vomiting, stiff neck, rash, light sensitivity, drowsiness, confusion
- Most resolved after discontinuation; in 15 symptoms returned when resumed LTG

JAMA, 2010.
Topiramate

- **Efficacy**
  - Partial, generalized, Lennox-Gastaut syndrome, infantile spasms

- **Adverse events**
  - Neurotoxicity, cognitive (language)
  - Weight loss, insomnia, renal stones

- **Advantages**: broad spectrum

- **Disadvantages**: slow titration as add-on therapy, cognitive
Topiramate – Protocol YD
50% Responders: Double-Blind vs. Baseline

**Randomized Dose Group**

- **Placebo (N=45)**: 18% with **p=0.620***
- **200 mg (N=45)**: 27% with **p=0.013***
- **400 mg (N=45)**: 47% with **p=0.027***
- **600 mg (N=46)**: 46%

*Comparison to placebo

Cognitive Outcomes: TPM vs. VPA

- Double-blind, randomized, parallel (17 variables)
- Add-on to CBZ in epilepsy patients

<table>
<thead>
<tr>
<th></th>
<th>TPM</th>
<th>VPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titration (mg/day/wk)</td>
<td>25 mg</td>
<td>150 mg</td>
</tr>
<tr>
<td>Completers</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>Dropouts</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Mean dose (mg/day)</td>
<td>251</td>
<td>1,384</td>
</tr>
</tbody>
</table>

- VPA > TPM on verbal memory

Titration = 12 wks; maintenance = 8 wks

Aldenkamp AP et al. 2000
Topiramate: Dosing and Administration

Adjunctive therapy, 2-16 yrs, mg/kg/day
- Starting dose ~1-3 nightly
- Increments 1-3 every 1-2 wks
- Target dose* 5-9

Monotherapy, children, 6-15 yrs
- Week 1 0.5 mg/kg nightly
- Week 2 0.5 mg/kg b.i.d.
- Week 3 1 mg/kg b.i.d.
- Target dose* 100 mg/day

If >100 mg needed, dose can be increased weekly by 50 mg/day

*Initial evaluation point
Zonisamide: Pivotal Clinical Trials

Study 2 & 3: % Responders

% of Patients

% Reduction in Seizures

- >25%: 55%
- >50%: 35%
- >75%: 27%
- >100%: 7.5%
Zonisamide: Oligohydrosis

- 13 reports during 11 yrs of marketing in Japan\textsuperscript{1,2}
  - Age: 1.6-17 yrs
  - Heat stroke requiring hospitalization, N=2
  - All cases reported during unusually hot summers
  - Doses: 5-15 mg/kg/day
  - No reported cases of decreased sweating in US and European development program
  - Body temperature should be carefully monitored in pediatric patients

\textsuperscript{1}Zonegran\textsuperscript{™}(zonisamide) prescribing information, Elan Pharmaceuticals.
\textsuperscript{2}Masuda Y et al. CNS Drug Reviews 4:341-360, 1998
Percentage Reduction in Partial Seizures During Treatment Period to 60 mg/kg/day

Median % Change from Baseline

LEV Placebo

26.8 %
p=0.0002

16.3 %
p<0.0001

43.3 %
Efficacy of Levetiracetam in Myoclonic Seizures

N=121; 12-65 yrs

- Refractory generalized epilepsy and myoclonic seizures
- LEV 3000 mg/day or placebo added to AEDs for 12 wks

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LEV</th>
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<tbody>
<tr>
<td>&gt;50% seizure reduction</td>
<td>23.3%</td>
<td>58.3%</td>
</tr>
<tr>
<td>Headache</td>
<td>23.3%</td>
<td>21.6%</td>
</tr>
<tr>
<td>Treatment-limiting adverse events</td>
<td>1</td>
<td>2</td>
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Noachtar S. Presented at: 26th International Epilepsy Congress; August 29, 2005; Paris, France.
## Adverse Events Overview

<table>
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<tr>
<th>Event</th>
<th>LEV (N=101)</th>
<th>Placebo (N=97)</th>
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<tbody>
<tr>
<td>Infection</td>
<td>28.7</td>
<td>28.9</td>
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<tr>
<td>Somnolence</td>
<td>22.8</td>
<td>11.3</td>
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<tr>
<td>Accidental injury</td>
<td>16.8</td>
<td>10.3</td>
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<tr>
<td>Vomiting</td>
<td>14.9</td>
<td>13.4</td>
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<tr>
<td>Headache</td>
<td>13.9</td>
<td>14.4</td>
</tr>
<tr>
<td>Anorexia</td>
<td>12.9</td>
<td>8.2</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>12.9</td>
<td>8.2</td>
</tr>
<tr>
<td>Hostility</td>
<td>11.9</td>
<td>6.2</td>
</tr>
<tr>
<td>Cough increased</td>
<td>10.9</td>
<td>7.2</td>
</tr>
<tr>
<td>Nervousness</td>
<td>9.9</td>
<td>2.1</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8.9</td>
<td>3.1</td>
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<tr>
<td>Dizziness</td>
<td>6.9</td>
<td>2.1</td>
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<tr>
<td>Agitation</td>
<td>5.9</td>
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<tr>
<td>Albuminuria</td>
<td>4.0</td>
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<td>Ecchymosism</td>
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<tr>
<td>Depression</td>
<td>3.0</td>
<td>1.0</td>
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</table>
Rufinamide

- Approved in November, 2008 as adjunctive treatment of seizures associated with Lennox-Gastaut syndrome
- Approval based on single pivotal trial (orphan drug status)
- Triazole derivative; exact mechanism of action unknown
  - Thought to regulate voltage dependent sodium channels
Rufinamide

- 34% protein bound; $T_{\text{max}}$ 6 hr fed, 8 hr fasted; half life 8-12 hr

- Hepatic metabolism to inactive metabolite

- Mild-moderate CYP3A4 induction, reduces oral contraceptive efficacy

- Few drug interactions (phenytoin and phenobarbital increase clearance by ~25%)

- Twice daily dosing (dose 400 to 2400 mg/day in 60 kg individual)

# AEs with Incidence ≥5% vs. Placebo in Subjects with Lennox-Gastaut Syndrome

<table>
<thead>
<tr>
<th>Total no. patients studied*</th>
<th>Rufinamide, % N=74</th>
<th>Placebo, % N=64</th>
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<tbody>
<tr>
<td>Somnolence</td>
<td>24.3</td>
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<td>Vomiting</td>
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<td>6.3</td>
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<td>Pyrexia</td>
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<td>Fatigue</td>
<td>9.5</td>
<td>7.8</td>
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<tr>
<td>Decreased appetite</td>
<td>9.5</td>
<td>4.7</td>
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<tr>
<td>Nasopharyngitis</td>
<td>9.5</td>
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<tr>
<td>Headache</td>
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<td>4.7</td>
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<tr>
<td>Rash</td>
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<td>1.6</td>
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<tr>
<td>Rhinitis</td>
<td>5.4</td>
<td>4.7</td>
</tr>
<tr>
<td>Ataxia</td>
<td>5.4</td>
<td>0.0</td>
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</table>

*Double-blind adjunctive therapy study in LGS; includes only AEs occurring at higher incidences with Rufinamide than placebo

Lacosamide in the Treatment of Complex Partial Seizures


Percentage of patients with at least 50 or 75% reduction in seizure frequency from baseline period to maintenance period
Intent to treat: SP667, SP754, SP755  *p<0.05; ** p<0.001

Responder Rates

Placebo (n=359)  LCM 200 mg/day (n=267)  LCM 400 mg/day (n=466)

50% Responders: 22.6%  34.1%*  39.7%**
75% Responders:  9.2%  13.5%  19.1%
Dr. Pellock has received grants/research support in excess of $10,000 and is a paid consultant as listed below. All grants, research support, consultant fees and honoraria are paid to Virginia Commonwealth University or the physician practice plan (MCV Physicians). Dr. Pellock has NO equity, stock or any other ownership interest in any of these companies.

<table>
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<th>Company</th>
<th>Advisory Board</th>
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<td>Catalyst</td>
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<td>Upshur Smith</td>
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</table>
Vigabatrin

- Approved January, 2009 for treatment of infantile spasms (orphan drug status)
  - Only drug approved in the US for treatment of IS
- Approved January, 2009 for treatment of patients with complex partial seizures who have not responded to several AEDs
- Previously approved years ago in other countries for partial seizures
Treatment Responders by Vigabatrin Dose and Etiology

Vigabatrin and Visual Field Defects

- Prevalence in adults ~30-50%
  - May be less in infants

- Concentric constriction: average peripheral field 65° (normal 90°); central vision not affected

- Typically asymptomatic

- Earliest occurrence ~11 months

- Appears irreversible, but does not progress

- Appears idiosyncratic, not clearly dose related

VGB (Sabril) Registry: 4 year Results (n=5487)

- Mean treatment duration: 9.9 months (IS shorter)
  - Total discontinued 59%
    - 2° reported visual deficits -15 (0.5%)
- Continuing patients
  - “visual loss” – 12
    - Visual acuity changes – 11
    - Perimetry change - 1
- Registry of 928 with cumulative, detailed vision results
  - 23% significant existing path (unrelated VCB) – (VF loss, disc pallor, ERG abnormal)
  - 2.6% vision effect possible/probable 2° VGB
Clobazam

- 1,5 benzodiazepine
  - In contrast to 1,4 benzodiazepines
  - Much less tachyphylaxis than 1,4 benzos
  - Acts like other BDZ to potentiate GABAergic inhibition
  - Rapid absorption 1-4 hrs
  - Highly lipophilic
  - 85% protein bound
  - No significant drug interactions
Clobazam

- Half life of parent compound 10 – 30 hrs
- Half life of active metabolite N-desmethyclobazam is 36 – 42 hrs
- Serum levels of little use
- Dose 10 – 80 mg/day in one or two doses
- Dose may need to be reduced with hepatic or renal insufficiency
- ? Risk of congenital malformations with BDZ
Mean percentage decreases (95% CI = confidence intervals) in weekly rate of seizures from the baseline to maintenance period (A) Drop seizures.

Ng Y et al. Neurology 2011;77:1473-1481
Stable dosages of clobazam for Lennox-Gastaut syndrome are associated with sustained drop-seizure and total-seizure improvements over 3 years.


Abstract

OBJECTIVE: To determine long-term safety and efficacy of adjunctive clobazam for patients with Lennox-Gastaut syndrome (LGS).

METHODS: Eligible patients from two randomized controlled trials (Phase II OV-1002 and Phase III OV-1012) were able to enroll in open-label extension (OLE) study OV-1004 beginning in December 2005 and received clobazam until they discontinued (mandatory at 2 years for patients outside the United States) or until study completion in March 2012. Patients in the United States could have received clobazam for 6 years before it became commercially available. Efficacy assessments included changes in rates of drop seizures and total seizures, responder rates (≥50%, ≥75%, or 100% decreases in seizure frequency vs. baseline), sustained efficacy over time, concomitant antiepileptic drug (AED) use, and global evaluations. Safety assessments included exposure to clobazam, laboratory assessments, physical and neurologic examinations, vital sign monitoring, electrocardiography monitoring, and adverse event reporting.

RESULTS: Of 267 patients who enrolled in the OLE, 188 (70%) completed the trial. Two hundred seven patients were from the United States, which was the only country in which patients could be treated with clobazam for >2 years. Forty-four patients were treated with clobazam for 5 years, and 11 for 6 years. Because of the low number of Year 6 patients, this group is not reported separately. Improvements in baseline seizure rates were very stable over the course of the study, with a median 85% decrease in drop seizures at Year 1, 87% at Year 2, 92% at Year 3, 97% at Year 4, and a 91% decrease for patients who had reached Year 5. Similar results were observed for total seizures (79% decrease at both Years 1 and 2, 82% decrease at Year 3, 75% decrease at Year 4, and 85% decrease at Year 5). Responder rates were also stable for the duration of the trial. Of patients who had achieved a ≥50% decrease in median drop-seizure frequency from baseline to Month 3, 86% still had that degree of drop-seizure reduction at Year 3 (and 14% lost their initial responses), and 47% were drop-seizure-free. Most patients who had achieved drop-seizure freedom in the original controlled trials remained drop-seizure-free in the OLE. Based on parents’ and physicians’ ratings of global evaluations, 80% of patients were "very much improved" or "much improved" after 3 years. Of the 43 patients with concomitant AED data who were treated for 5 years, 30% increased, 19% decreased, and 51% had no change in numbers of AEDs versus their Week 4 regimens. The mean modal clobazam dosage was 0.90 mg/kg/day at Year 1 and 0.97 mg/kg/day at Year 5, suggesting that study patients did not need significant increases in dosage over time. The safety profile was what would be expected for clobazam for LGS patients over a 5-year span, and no new safety concerns developed over time.

SIGNIFICANCE: In this largest and longest-running trial in LGS, adjunctive clobazam sustained seizure freedom and substantial seizure improvements at stable dosages through 3 years of therapy in this difficult-to-treat patient population. A PowerPoint slide summarizing this article is available for download in the Supporting Information section here.
Median reduction in total seizure frequency on antiepileptic drug vs placebo

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percent Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine</td>
<td>30</td>
</tr>
<tr>
<td>Topiramate</td>
<td>20</td>
</tr>
<tr>
<td>Felbamate</td>
<td>25</td>
</tr>
<tr>
<td>Rufinimide</td>
<td>10</td>
</tr>
<tr>
<td>Clobazam</td>
<td>60</td>
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</tbody>
</table>
A first in class selective AMPA antagonist.

Studied in three add-on trials of partial onset seizures.

Efficacy for seizure reduction about 40%.

No serious toxicity seen.
Perampanel

(A) Median percent change in partial-onset seizure frequency and SG seizure frequency per 28 days (Double-blind phase vs. Baseline) and (B) 50% responder rates for all partial-onset seizures and SG seizures (patients experiencing ≥50% reduction in seizure frequency per 28 days during the Maintenance Period vs. Baseline) for patients who completed the Maintenance Period of studies 304 or 305 on perampanel 8 mg or perampanel 12 mg (actual [last] dose analysis, excluding patients from Latin America region). SG, secondarily generalized.

Epilepsia © ILAE
(A) Median percent change in seizure frequency per 28 days (treatment versus Baseline) and (B) 50% responder rates (patients experiencing ≥50% reduction in seizure frequency per 28 days) for patients who were randomized to perampanel 8 or 12 mg in the phase III studies (studies 304, 305 and 306), completed the Maintenance Period of the three phase III on the target dose, and who had an actual (last) dose of perampanel 12 mg during the extension study blinded Conversion Period or weeks 1–13 of the extension study Maintenance Period (actual [last] dose analysis, excluding patients from Latin America region).

Epilepsia © ILAE
Extended Release Formulations

- OXC -> Oxtellar XR
- TPM -> Trokendi XR
- Qudexy XR
Study Reveals Concerns About Switching From Branded to Generic Antiepileptic Drugs

Studies may reveal why some patients who switch to generic AEDs lose seizure control or have adverse events.
Medical Marijuana and Epilepsy

- Anecdotal reports – few negative
- Overall efficacy, safety, dosing not defined
- “Charlotte’s Web” – cannabidiol (CBD) – Weed (CNN)
- Legal in 15 states
- AES: support well designed clinical research
- EF: Change from Schedule I (DEA) to allow research
- FDA: Granted orphan status for Epidiolex (GW) – Dravet, LGS, Phase 1, CBD, 5 sites
- No trial has yet demonstrated efficacy (Willner, Medscape, 2014)
# Anticonvulsant Drugs Marketed in the U.S.

<table>
<thead>
<tr>
<th>Year</th>
<th>Drug Name</th>
<th>Company</th>
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<tbody>
<tr>
<td>1912</td>
<td>Phenobarbital (Luminal®)</td>
<td>Winthrop</td>
</tr>
<tr>
<td>1935</td>
<td>Mepobarbital (Mebaral®)</td>
<td>Winthrop</td>
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<td>1938</td>
<td>Phenytoin (Dilantin®)</td>
<td>Parke-Davis</td>
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<td>1947</td>
<td>Mephenytoin (Mesantoin®)</td>
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<td>1954</td>
<td>Primidone (Mysoline®)</td>
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<td>Methsuximide (Celontin®)</td>
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<td>Diazepam (Valium®)</td>
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<td>Carmazepine (Tegretol®)</td>
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<td>1975</td>
<td>Clonazepam (Klonopin®)</td>
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<td>Valproic acid (Depakene®)</td>
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<td>Felbamate (Felbatol®)</td>
<td>Carter-Wallace</td>
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<td>Gabapentin (Neurontin®)</td>
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<td>Lamotrigine (Lamictal®)</td>
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<td>Levetiracetam (Keppra®)</td>
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<td>Vimpat (Lacosamide®)</td>
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<td>ACTH (Acthar, IS)</td>
<td>Questcor</td>
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<td>Parampanel (Fycompa)</td>
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<td>Eslicarbazepine (Aptiom)</td>
<td>Sunovion</td>
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