From Bench to Pipeline to Patients: New Developments in Anticonvulsant Drug Development

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Disclosure

None
Learning Objectives

• To understand the drug discovery process employed by the Anticonvulsant Drug Development (ADD) Program

• To learn about a new anticonvulsant drug that is in the discovery pipeline
The Problem

• In the early 70’s approximately 25-40% of patients with epilepsy were considered to be refractory to existing antiepileptic drugs (AEDs)
• Pharmaceutical companies were not investing in AEDs
A Solution: The Anticonvulsant Drug Development (ADD) Program

Preclinical efficacy and safety studies (two species)

Clinical trials in volunteers and patients with epilepsy

FDA approval and marketing

> 35,000 compounds tested to date
The good news: the ADD program has contributed to the success of 14 compounds

<table>
<thead>
<tr>
<th>Year</th>
<th>Compound</th>
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<tbody>
<tr>
<td>1993</td>
<td>Felbamate*</td>
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<tr>
<td>1994</td>
<td>Gabapentin</td>
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<tr>
<td>1994</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>1996</td>
<td>Fosphenytoin</td>
</tr>
<tr>
<td>1996</td>
<td>Topiramate*</td>
</tr>
<tr>
<td>1997</td>
<td>Tiagabine</td>
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<tr>
<td>1999</td>
<td>Levetiracetam</td>
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<tr>
<td>2000</td>
<td>Zonisamide</td>
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<tr>
<td>2000</td>
<td>Oxcarbazepine</td>
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<tr>
<td>2005</td>
<td>Pregabalin</td>
</tr>
<tr>
<td>2008</td>
<td>Rufinamide*</td>
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<tr>
<td>2008</td>
<td>Lacosamide*</td>
</tr>
<tr>
<td>2009</td>
<td>Eslicarbazepine acetate</td>
</tr>
<tr>
<td>2011</td>
<td>Ezogabine*</td>
</tr>
</tbody>
</table>

*ADD Program played a significant role in identification and characterization.
More Good News: AEDs in the pipeline

- Brivaracetam
- 2-Deoxy-glucose
- Ganaxolone
- Huperzine A
- JZP-4
- Perampanel
- Propylisopropylacetamide
- T-2000
- Tonabersat
- Valnoctamide
- Valrocemide
- YKP-3089


Bialer et al., Epilepsy Res. 2010, 92:89-124
The Bad News

- 25-40% of patients are refractory to existing AEDs
  - PHARMACORESISTANCE
  - STATUS EPILEPTICUS remains difficult to treat
- We cannot prevent the development of epilepsy in patients at risk
  - EPILEPTOGENESIS
In Vitro Screens

In Vivo Screens

In Vivo Models

MRICD

Validation

Block convulsive SE
In vivo neuroprotection
Prevent cognitive impairment

Neuroprotective in organotypic hippocampal slices

Block electrographic SE, neuroprotective, halt/slow epileptogenesis?

2 compounds
sec-Butyl-propylacetamide (SPD): A Broad Spectrum Anticonvulsant Derivative of VPA

White, H.S. et al., Epilepsia, in press
SPD is active against a variety of acute and chronic seizure models

- Frings Audiogenic Seizures
- 6 Hz psychomotor seizure (mice)
- Maximal electroshock seizure (mice & rats)
- Metrazol-induced seizure (mice & rats)
- Picrotoxin-induced seizure (mice-Pic)
- Bicuculline-induced seizure (mice-Bic)
- Corneal kindled mouse
- Hippocampal kindled rats
- **Wide protective indexes** \( (PI= TD_{50}/ED_{50}) \) ranging between 4.4-7.7

White, H.S. *et al.*, *Epilepsia*, in press
SPD prevents pilocarpine SE-induced cognitive impairment

White, H.S. et al., Epilepsia, in press
SPD reduces pilocarpine SE-induced FluoroJade B staining

Pilocarpine: Considerable Neuronal Cell Death

Pilocarpine + SPD: Partial Neuroprotection

Pilocarpine + SPD: Complete Neuroprotection

White, H.S. et al., Epilepsia, in press
SPD does not protect against NMDA-induced neural cell death

White, H.S. et al., Epilepsia, in press
SPD can terminate soman-induced status epilepticus

White, H.S. et al., Epilepsia, in press
SPD can terminate soman-induced status epilepticus soon after administration

White, H.S. et al., Epilepsia, in press
SPD can terminate soman-induced electrographic status epilepticus in guinea pig

White, H.S. et al., Epilepsia, in press
Summary and Conclusions

• The ADD program has a successful history of identifying and characterizing novel anticonvulsants.
• There are a number of anticonvulsants in the pipeline.
• SPD is a broad spectrum and potent new anticonvulsant.
• SPD confers neuroprotection and preserves cognitive function following SE by halting seizures.
• SPD can terminate soman-induced SE rapidly.
• Continued development of SPD is warranted.
Impact on Clinical Care and Practice

- If approved for human use, SPD may be an alternative treatment for status epilepticus
- Recently approved compounds can give the physician and patient with epilepsy additional treatment options
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