Is industry prepared to meet challenges of better epilepsy treatments?

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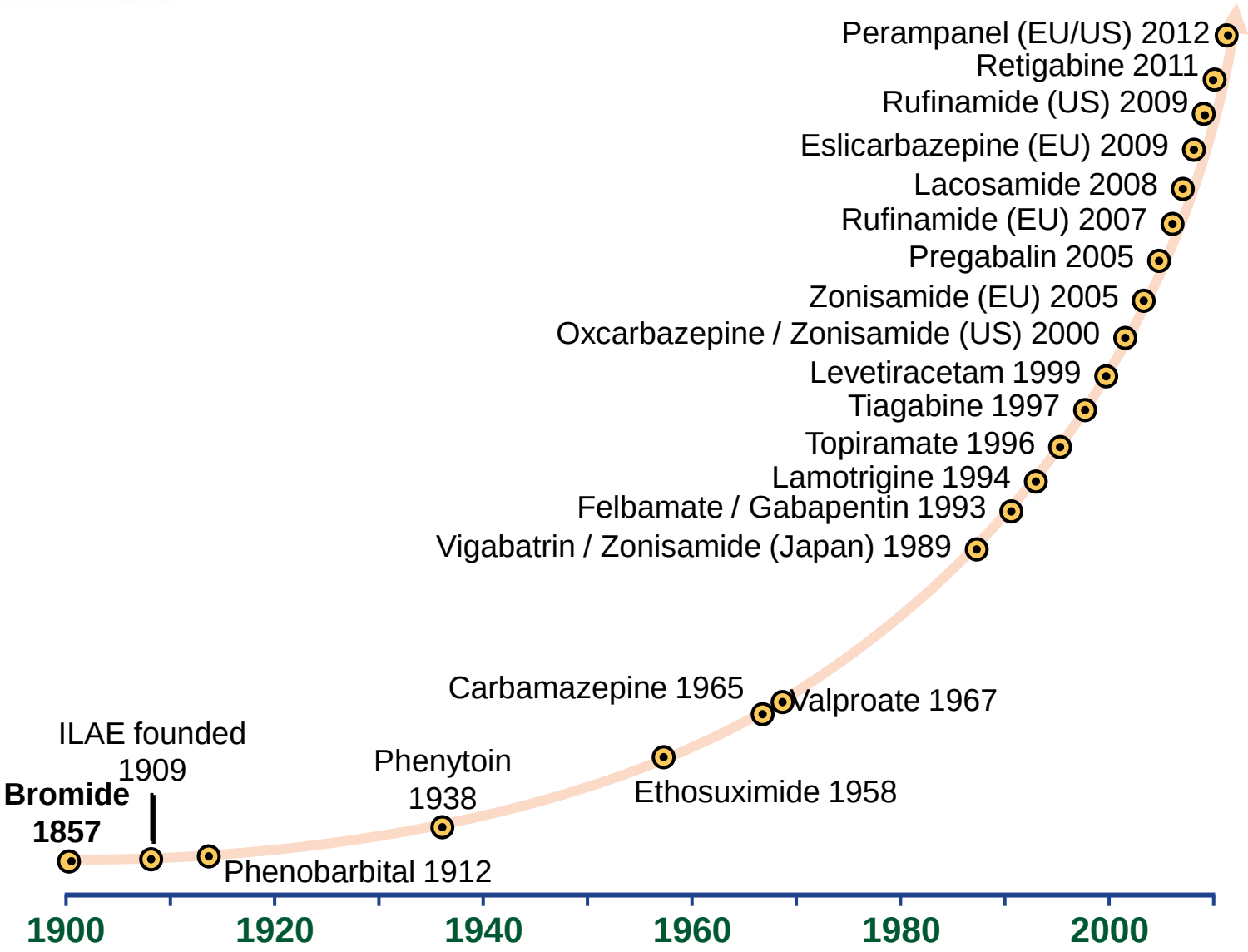
hhc

human health care

History of pharmacological epilepsy treatment



Arzimanoglu et al., Epileptic Disord (2010) 12: 3-15

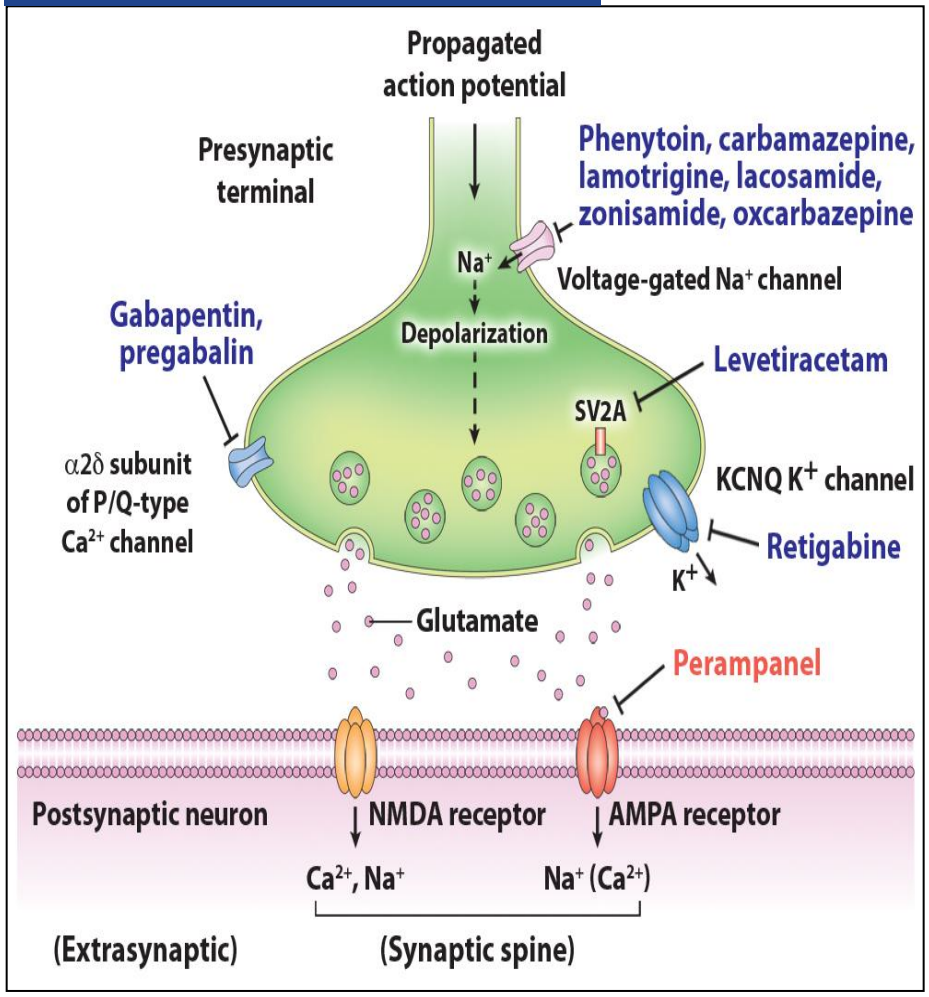
Continued need for drug development to cater for unmet need?

- Huge unmet need
  - (similar for most Neurological diseases)
- Up to **40%** of patients remain uncontrolled despite treatment
- Changing drug therapy in previously uncontrolled patients can result in seizure reduction or seizure freedom
- In uncontrolled patients, **37%** of all drug introductions resulted in a worthwhile improvement, including **16%** that resulted in seizure freedom[1]

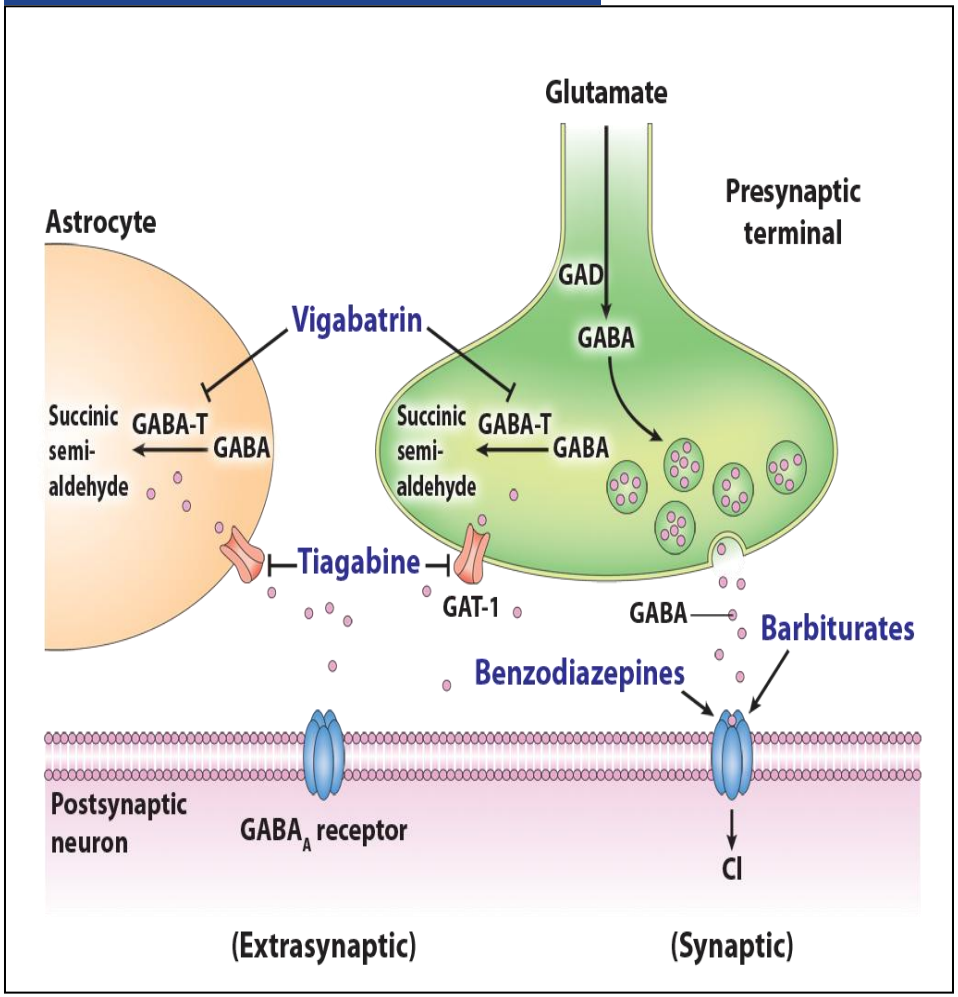
1. Ann Neurol. Luciano AL, Shorvon SD. Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. 2007 Oct;62(4):375-81

AED targets – primary MOA

Excitatory synapse



Inhibitory synapse



Adapted from *Bialer & White, Nature Rev Drug Disc (2010) 9: 68--82*

Eisai's commitment to Neurology

- **Alzheimer's Disease**
  - **Donepezil**
  - **Amyloid lowering therapies in clinical development**
- **Epilepsy**
  - **Eslicarbazepine, Rufinamide, Zonisamide (2nd Gen AEDs)**
  - **Perampanel (3rd Gen AED)**
- **Insomnia**
  - **Eszopiclone (Japan)**
- **Pain/Neuropathy**

Perampanel – Novel mechanism

Mechanism of action

- **A highly selective non-competitive AMPA receptor antagonist**
- **First-in-class**
  - ✓ Has benefit as addition to existing mechanisms of anti-epilepsy drugs

Rogawski (2013) Acta Neurol Scand Suppl, 197:9-18

Rogawski & Handa (2013) Acta Neurol Scand Suppl, 197:19-24

Efficacy

- 40% median reduction in partial onset seizure frequency vs. 13% with placebo
- 40% responder rate vs. 17% with placebo
- Onset of action in week 2
- Demonstrated efficacy on secondarily generalized seizures

Steinhoff et al. (2013) Epilepsia epub May 10 doi: 10.1111/epi.12212

Safety & PK

- Well tolerated
- No need for blood monitoring
- Long half-life

Serratosa et al. (2013) Acta Neurol Scand Suppl, 197: 30-35

Steinhoff et al. (2013) Epilepsia epub May 10 doi: 10.1111/epi.12212

Drug delivery

- Once-daily oral tablets (2 -12 mg)
- Weekly or bi-weekly titration from 2mg to effective dose
- Simple dosing instructions

Satlin et al. (2013) Acta Neurol Scand Suppl, 197: 3-8

Perampanel: Treatment of partial onset seizures in patients aged 12 years and older

human health care

Perampanel Story

1998

Drug Discovery

Clinical development

Regulatory process

EML

2012

Launch

UCL

Pre-clinical develop-ment

Data analysis

EKC

Production

Market Access

Media relation

Medical

Training

Marketing

Beyond Epilepsy treatment

- **Aberrant neuronal firing being described in other neurological disorders**
  - **Dementia**
  - **ADHD**
  - **Neuropathic pain**
  - **Migraine**
  - **Head injury**
- **Use of AEDs in other neurological conditions not well defined**
- **Selective agents with defined MoAs and better side effect profiles may have utility in broader CNS indications**

Challenges for Neuroscience research

- **Industry scaling back commitment to Neuroscience research**
  - **Changes in business models: virtualisation, partnerships, patent box**
  - **Change in therapeutic focus areas: oncology, metabolic**

- **Development costs/R&D Efficiency**
  - **Utility/Predictivity of Animal Models**
    - **Epilepsy, AD etc**
  - **Probability of Success (Ph1-Launch) – 5-8%**
  - **Only 20% of patients anticipated to be on 3rd generation or later AEDs by 2021**
    - **Challenges of performing monotherapy trials**
  - **Challenging development for novel mechanisms in neurology**
  - **Peak sales of innovative products trending downwards**

Scannell et al., Nature Rev Drug Disc (2012) 11: 191-200; Berggren et al., Nature Rev Drug Disc (2012) 11: 435-436

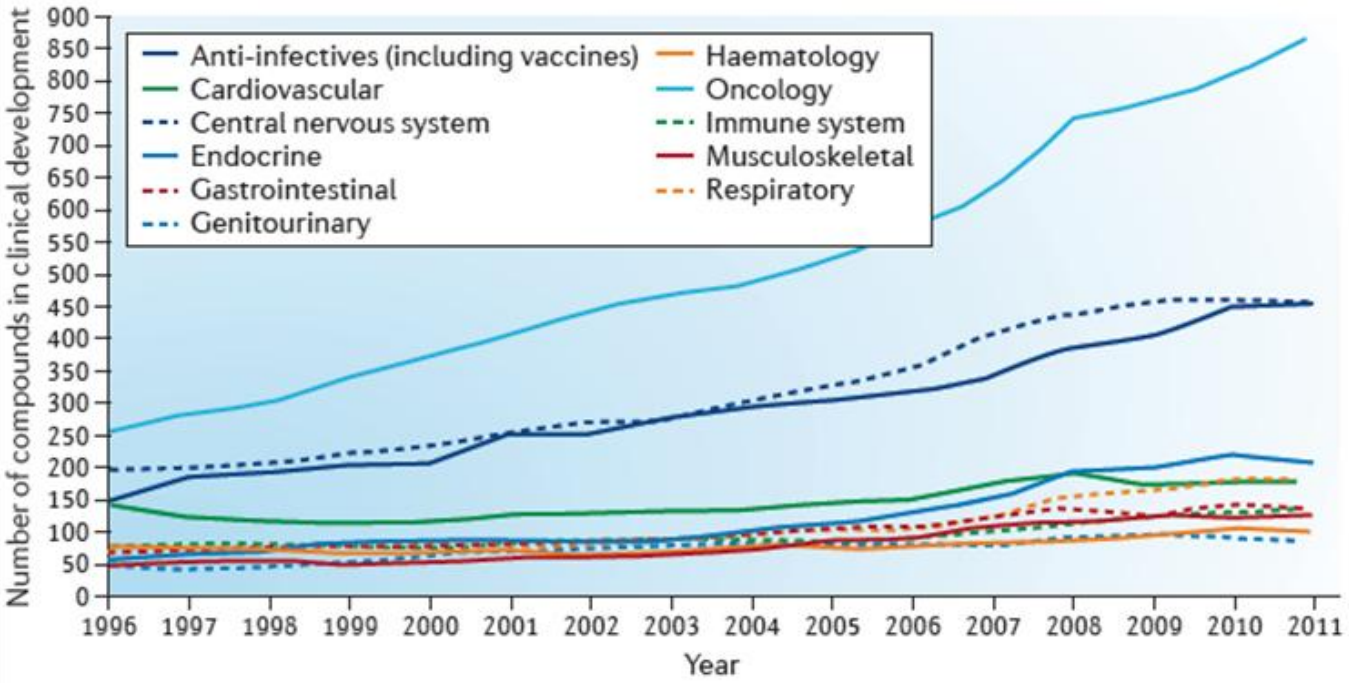


Figure 1 | **Compounds in clinical development by therapeutic area.** The figure includes all innovative compounds between Phase I and Phase III development with historical progression data available. The smallest therapeutic areas (dermatology, sensory, diagnostics and imaging, and other) were excluded for clarity. Source: Pharmaprojects Pipeline, 2011, Citeline, an Informa business; see Supplementary information S1 (box) for details of data sources and analysis.

Scannell et al., Nature Rev Drug Disc (2012) 11: 191-200; Berggren et al., Nature Rev Drug Disc (2012) 11: 435-436

Challenges for Neuroscience research

- **Patent terms**
  - **20 year patent term**
    - **to Approval can be ~10 years**
  - **…….but clinical trials (PhI-III) for neurological diseases can take >5 years plus approval times**

- **Regulatory/Reimbursement requirements**
  - **Benefit over existing treatments, severe populations, ethics of monotherapy?**
  - **lower risk appetite for neurological products?**
  - **Value for Payers and patients over existing treatments**
  - **Genericised markets containing highly effective agents**
    - **challenges for novel mechanisms to gain traction**

- **Regional differences in approval methods**
  - **CNS drugs: DEA scheduling in the US**
  - **adds time post-FDA approval to launch**

Overcoming the challenges

- **Continued efforts to understand underlying disease processes in epilepsy and other neurological diseases**

- **Patient selection/stratification based on biomarkers, disease profile**
  - **Seizure phenotype, genetic markers,**

- **Use of novel clinical trial designs**
  - **adaptive, 'withdrawal to monotherapy'**

Therapeutic Innovation - How

- **Open Innovation – Novel targets**
  - **Maximizing capabilities in industry and academia**
- **Partnerships**
  - **Academic-Industry Partnerships**
    - **e.g. IMI (EU-EFPIA), Wellcome Trust/MRC, CRUK in oncology, Eisai-UCL**
    - **Pre-competitive consortia to move the science forward**
  - **Industry Partnerships: Eisai-Bial, Scottish Epilepsy, Specialist CROs**
- **Risk sharing**
  - **Across disease phenotypes: epilepsy phenotypes to gain wider approval**
  - **Collaboration on risky targets, revenue sharing on launch**
- **Beyond Epilepsy**
  - **Novel MoAs/Improved Side effect profiles: broader utility in neurological diseases?**