I am going to outline the history of the development of some antiepileptic drugs, including valproate, and discuss its pharmacological actions. The pharmacology of valproate is very complicated, and this will be a simplified version of current knowledge.
These are my potential conflicts of interest in this area.
The effective management of epileptic seizures goes back to the 19th century, when Sir Charles Locock introduced the use of potassium bromide.
Locock was, among other things, President of the Royal Medical & Chirurgical Society (now, after merger with other societies, the Royal Society of Medicine). He presided at a meeting of the Society on Tuesday 11 May, 1857. Dr Edward H Sieveking described 52 cases of epilepsy. He included details of the age and sex distribution of the cases, of the modes of presentation, and the associated features, thought to contribute to the cause. He described treatment by changing diet and lifestyle (“dietetic and regiminal treatment”) and said that "the main indications which should guide us, are to remove local irritation by counterirritants, to promote the healthy action of the secerment [i.e. secretory] organs, and to give a tone to the constitution by vegetable and metallic roborants." He also noted that zinc salts were ineffective.
In the discussion that followed, Locock referred to his own use of potassium bromide in cases of hysteria, and gave details of one case of hysterical catamenial epilepsy, in which potassium bromide, given for 14 days, and later for only one week, before each menstrual period had resolved the problem. He then noted that "Out of fourteen or fifteen cases treated by [potassium bromide], only one had remained uncured." This led to the more general use of potassium bromide in the management of epileptic seizures.
Here the use of potassium and ammonium bromides in epilepsy is described in the 20th edition of Martindale & Westcott’s *Extra Pharmacopoeia* (1932).
Alfred Hauptmann was a German physician who was in charge of a ward full of patients with epilepsy. His living quarters were immediately above the ward, and he was kept awake at night by the sounds of patients having seizures. Hoping to get a good night’s sleep, he gave his patients phenobarbital, which had recently come available. He discovered that not only did they sleep well overnight, but that their seizures abated during the following day as well. He went on to study it carefully and phenobarbital was introduced as a treatment for epileptic seizures. It gradually displaced potassium bromide, which was less effective and caused severe adverse reactions, such as bromism.
He described his experience in this article, "Luminal bei Epilepsie”, published in the *Münchener medizinische Wochenschrift* (1912, 59: 1907-9). Luminal was a brand name for phenobarbital.
Tracy J Putnam was a physician working in the New York Neurological Institute at Columbia University. He decided to look for other compounds, similar in chemical structure to phenobarbital, that might be effective in epilepsy.
One of the compounds he studied was called phenytoin (diphenylhydantoin; brand name Dilantin).
Putnam and his colleague H Houston Merritt (Science 1937; 85: 525-6) showed that phenytoin suppressed seizure activity in the brains of experimental animals.
They then introduced phenytoin into clinical practice (JAMA 1938; 111(12): 1068-73).
Like many important discoveries in the history of pharmacology, valproate was not developed by any "rational strategy," but its anticonvulsant activity was serendipitously discovered by Pierre Eymard in France in 1962. Valproic acid (VPA; valproate; di-n-propylacetic acid, DPA; 2-propylpentanoic acid, or 2-propylvaleric acid) was first synthesized in 1882, by Burton [1], but there was no known clinical use until its anticonvulsant activity was fortuitously discovered by Eymard. Because valproic acid is a liquid, it was used as a lipophilic vehicle to dissolve water-insoluble compounds during preclinical drug testing. As part of his thesis in 1962, Eymard had synthesized a number of khelline derivatives in the laboratory of G. Carraz at the School of Medicine and Pharmacy in Grenoble, France [2]. Two colleagues, H. Meunier and Y. Meunier, working for a small company, Berthier Laboratories, in Grenoble, had used valproate for a long time as a vehicle for dissolving a bismuth salt. So the three scientists Eymard, Meunier and Meunier had the idea to use this vehicle also for dissolving some of the khelline derivatives synthesized by Eymard. In order to evaluate the pharmacological activities of the khelline derivatives, Carraz proposed to test the most active derivative in the pentylentetrazole (PTZ) seizure test. By doing this, the researchers found that the vehicle, valproate, alone exerted an anticonvulsant effect.

This is the story of how valproate was discovered.
There are three main formulations: valproic acid, sodium valproate (the sodium salt of the acid), and a combination of the two, called divalproex sodium or valproate semisodium. Valproic acid and divalproex sodium are both converted to sodium valproate in the body.
Two other compounds, valpromide and valnoctamide, are not as effective as valproate.
This shows the major ways in which valproate is metabolized (broken down) in the body.
Today four companies are listed in the electronic Medicines Compendium as marketing 29 different formulations of valproate and its congeners (from https://www.medicines.org.uk/emc/search?q=valproate).
Here are some examples. Epilim and Depakote are the most commonly dispensed formulations in the UK. Other branded products, not listed in the Compendium, include Convulex, Kentlim, Orlept, Syonell, and Valpal.
They are mostly licensed for the treatment of generalized epilepsy, partial epilepsy, or other forms of epilepsy. However, Depakote is licensed for the treatment of manic episodes in bipolar affective disorder (commonly called manic-depression) and Episenta is licensed for both that and epilepsy.
These are proposed mechanisms whereby valproate reduces the frequency of seizures ...
… also shown here. One of its metabolites, Δ2,3-VPE (2-n-propylpent-2-enoic acid), also has some therapeutic actions.
The list of adverse effects and adverse reactions that valproate can cause is very long. On the next few slides they are listed according to whether they are very common …
Adverse effects and adverse reactions

Common

- Hepatobiliary disorders
  - Liver damage
- Gastrointestinal disorders
  - Vomiting, gingival hyperplasia, stomatitis, gastralgia, diarrhoea
- Nervous system disorders
  - Extrapyramidal disorder, stupor, somnolence, convulsion, memory impairment, headache, nystagmus
- Psychiatric disorders
  - Confusional state, hallucinations, aggression, agitation, altered attention
- Metabolism
  - Hyponatraemia, weight increased
- Blood disorders
  - Anaemia, thrombocytopenia
- Skin disorders
  - Hypersensitivity, alopecia, nail and nail bed disorders
- Reproductive system
  - Dysmenorrhea
- Vascular disorders
  - Haemorrhage
- Ear disorders:
  - Deafness
- Renal and urinary disorders
  - Urinary incontinence

... common ...
Adverse effects and adverse reactions

Uncommon

- **Gastrointestinal disorders**
  - Pancreatitis

- **Nervous system disorders**
  - Coma, encephalopathy, lethargy, reversible parkinsonism, ataxia, paraesthesia, aggravated convulsions

- **Endocrine disorders**
  - Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism

- **Blood disorders**
  - Pancytopenia, leucopenia

- **Skin disorders**
  - Angioedema, rash, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth)

- **Reproductive system**
  - Amenorrhea

- **Vascular disorders**
  - Vasculitis

- **Renal and urinary disorders**
  - Renal failure

- **General disorders**
  - Hypothermia, peripheral oedema

- **Musculoskeletal disorders**
  - Reduced bone mineral density, osteopenia, osteoporosis and fractures

- **Respiratory**
  - Pleural effusion

... uncommon ...
Adverse effects and adverse reactions

**Rare**

- **Nervous system disorders**
  - Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder
- **Psychiatric disorders**
  - Abnormal behaviour, psychomotor hyperactivity, learning disorder
- **Metabolism**
  - Hyperammonaemia, obesity
- **Endocrine disorders**
  - Hypothyroidism
- **Blood disorders**
  - Bone marrow failure, abnormal coagulation tests, Myelodysplasia syndrome
- **Skin disorders**
  - Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, DRESS syndrome
- **Reproductive system**
  - Male infertility, polycystic ovaries, gynaecomastia
- **Eye disorders**
  - Diplopia
- **Renal and urinary disorders**
  - Enuresis, tubulointerstitial nephritis, reversible Fanconi syndrome
- **Musculoskeletal disorders**
  - Rhabdomyolysis
- **Autoimmune**
  - Lupus-like syndrome
Valproate can also take part in a range of adverse drug-drug interactions, in which the effects of valproate are either increased (left) or reduced (right) by other medicines. Several of the other drugs listed here are also antiepileptic drugs.

<table>
<thead>
<tr>
<th>Increased effect</th>
<th>Reduced effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants</td>
<td>Nimodipine</td>
</tr>
<tr>
<td>Antipsychotic drugs</td>
<td>Phenobarbital</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Primidone</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Propofol</td>
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<tr>
<td>Felbamate</td>
<td>Rufinamide</td>
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<tr>
<td>Lamotrigine</td>
<td>Temozolomide</td>
</tr>
<tr>
<td>MAO inhibitors</td>
<td>Zidovudine</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Phenytoin</td>
</tr>
</tbody>
</table>
Several antiepileptic drugs can cause major congenital malformations in babies if they are taken by pregnant women.
The risks are shown here; valproate carries the highest average risk of all antiepileptic drugs (10%; top panel) and the risk increases with increasing daily dosage (bottom panel).
These are some of the malformations that can occur.
Many mechanisms have been proposed. For example, valproate may interfere with DNA function by inhibiting histone deacetylase …
… the relevance of which is illustrated in this diagram.
Possible mechanisms of the teratogenic action of valproate

1. DNA replication or transcription
   Inhibition of histone deacetylase
2. Synthesis and/or function of growth factors
3. Synthesis and/or function of integrins
4. Angiogenesis

Other mechanisms have been proposed (2-4) ...
… and effects on growth factors, integrins, and angiogenesis (formation of blood vessels) may be linked, as shown here.
Altered apoptosis (programmed cell death) is another possible mechanism...

### Possible mechanisms of the teratogenic action of valproate

1. DNA replication or transcription
   - Inhibition of histone deacetylase
2. Synthesis and/or function of growth factors
3. Synthesis and/or function of integrins
4. Angiogenesis
5. Cell death or damage (e.g. altered apoptosis)
… as shown here.
And yet other mechanisms (6-8) are possible.

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<td>6. Chondrogenesis</td>
</tr>
<tr>
<td>7. Hypervitaminosis A</td>
</tr>
<tr>
<td>8. Activation of extracellular signal-regulated kinase (ERK)</td>
</tr>
</tbody>
</table>
This is the 2016 advice given by the UK’s Medicines and Healthcare products Regulatory Agency (MHRA) on the use of valproate in pregnant women (https://www.covwarkpt.nhs.uk/download.cfm?doc=docm93jjjm4n1752.pdf&ver=2310).
Some conclusions

1. Drugs can be discovered in different ways, for example:
   - Chance
   - Putting compounds through screening tests
   - Pharmacological reasoning
2. Several antiepileptic drugs are teratogenic; valproate most of all
3. Evidence that made this clear was available, had it been analysed, by 2005, emphasizing the importance of cumulative meta-analysis
4. Many different mechanisms might be responsible