Anxiolytics

- Anxiolytic means anti-anxiety
- SSRIs are the most prescribed anxiolytics, but benzodiazepines are the most common "targeted" anxiolytics. In this context, targeted means that benzodiazepines are specifically for anxiety, whereas SSRIs were originally for depression.
- Barbiturates, alcohol, and opiates relieve anxiety, but have side effects and addiction problems

Anxiolytics

- Benzodiazepines relieve anxiety for three reasons:
  - Antipunishment effect
  - Relief of anxiety symptoms
    - Nausea, palpitations, dry mouth, trembling, sweating, muscle tension
  - General sedation
    - What is the difference between antipunishment effect and general sedation?

Mind-Body Parallel

- Many anxiolytics relieve both the physical and mental aspects of anxiety. Beta blockers such as propranolol provide a good example. Propranolol primarily attacks the physical symptoms of anxiety (palpitations, trembling, sweating), but this seems to inhibit the positive feedback loop that can exacerbate anxiety.

Antipunishment Effect

- Easily tested in animals
- Enables fearful people to board a plane
- Causes normal people to take excessive risks:
  - Talk out of turn, sing loud
  - Fight
  - Unprotected sex
  - Relapse into using other drugs
  - Drive dangerously (these drugs tend to impair driving while simultaneously impairing judgment, a double whammy)

Anxiolytics

Uses of anxiolytics:

- Generalized anxiety disorder (GAD)
- Social anxiety disorder (SAD), social phobia (SSRIs are strongly preferred)
- Panic disorder
- Phobias (SSRIs and therapy are strongly preferred)
- Surgical sedation: to potentiate anesthetics, as anesthetics, and to reduce anxiety prior to the procedure

History of Anxiolytics

1500 BCE or earlier: **Opium**

Opium was originally harvested in and around India.
Medicinal use of opium features prominently in ancient Indian scientific and religious texts.
Opium contains **morphine** and **codeine**, plus other things.

6000 BCE or earlier: **Alcohol**

6000 BCE: Mead-like beverage in China. Beer-like beverages in the Middle East at a similar era.
Beer becomes widespread, it has 2 to 8% ABV. Beer is full of vitamins, nutrients, and calories. It is a good way to preserve grain for the winter.
2000 BCE or earlier: Grape wine is widespread.

History of Anxiolytics

1857: **Bromide salts**

0.5 grams of potassium bromide, taken 3 times a day, is quite sedating. By the late 1800's, single hospitals were using several tons of potassium bromide per year.

1800's: **Paraldehyde, chloral hydrate**

These drugs are simple chemicals, like ethanol, and they have many poorly understood mechanisms, like ethanol. Large doses are required, nausea is almost guaranteed.

1904: **Barbiturates**

1904 saw a drug company launch barbital (diethyl barbituric acid, Veronal). It immediately saw widespread clinical use.

History of Anxiolytics

Barbiturates were **extremely valuable** drugs from the time of their invention to about 1950. During that time, barbiturates were by far the most effective and least toxic treatments for:

- Anxiety
- Insomnia
- Seizures
- Schizophrenia (arguable)
- Mania (arguable)

History of Anxiolytics

1912-1960: **Barbiturate conveyor belt**

Phenobarbital was launched for clinical use in 1912. This sparked off a "conveyor belt" phenomenon of barbiturate launches, controversies, and then withdrawals.

1956: **Quaalude (methaqualone)**

An especially euphoric sedative.

1960's-1980's: **Benzodiazepines**

1960: **Librium** (chlordiazepoxide) is approved. This is the first benzodiazepine tranquilizer.

1963: **Valium (diazepam)** is approved. Valium becomes the most prescribed drug in America from 1969 to 1982.

Barbiturate Problems

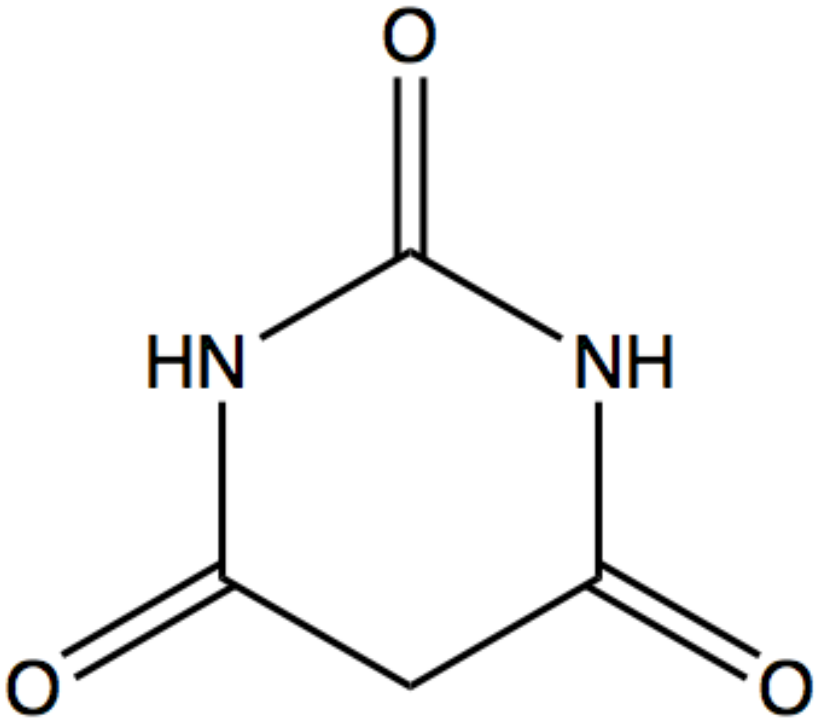
Barbiturate overdose is often fatal. This is because it causes **respiratory depression** (just like opioid overdose).

Barbiturates cause alcohol-like euphoria, and thus are often abused.

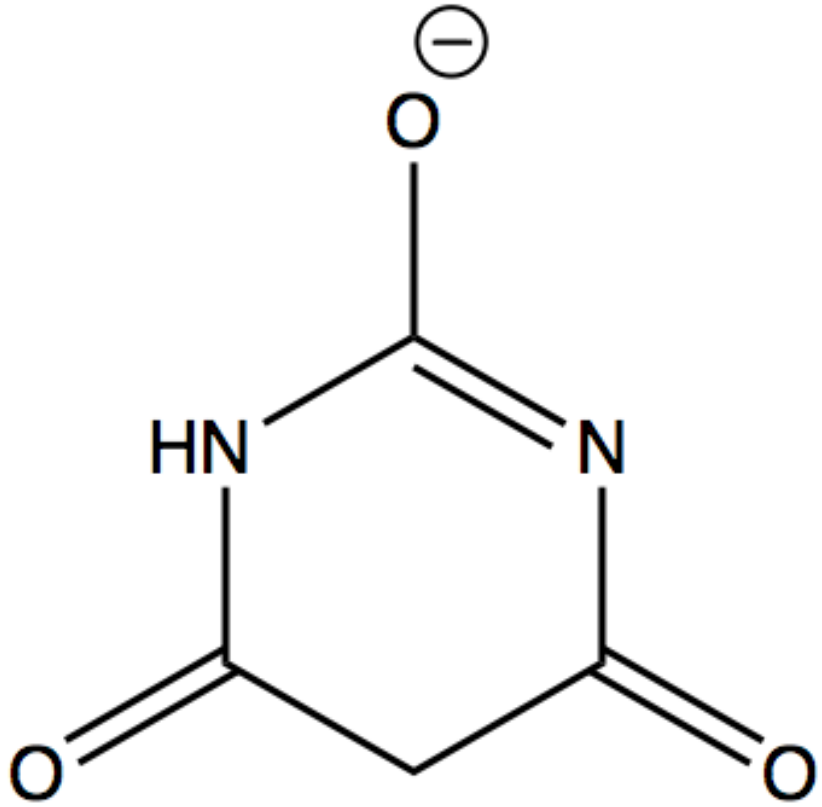
Barbiturates vs. Benzodiazepines

Barbiturates: Can open the GABA-A chloride channel in the absence of GABA.

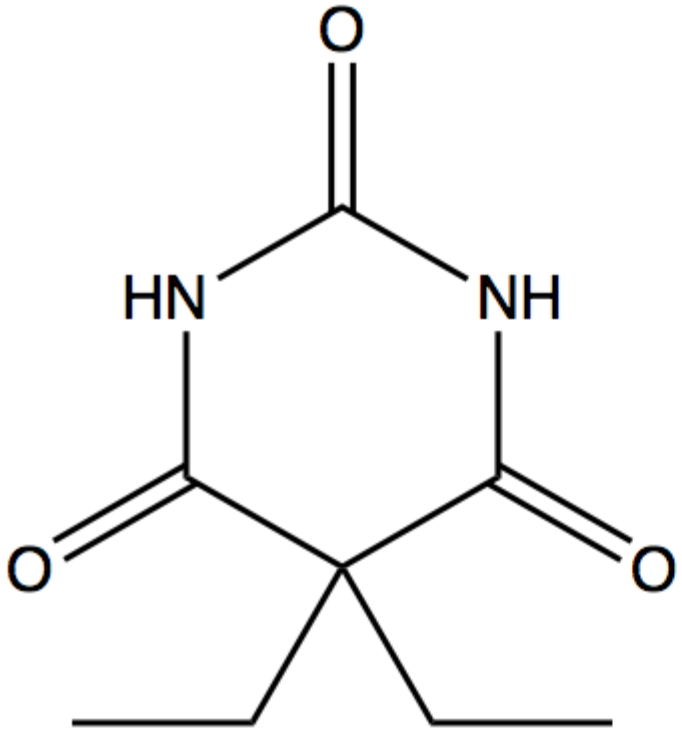
Benzodiazepines: Cannot open the GABA-A chloride channel without GABA. GABA is necessary for a benzodiazepine to act.



Barbituric acid

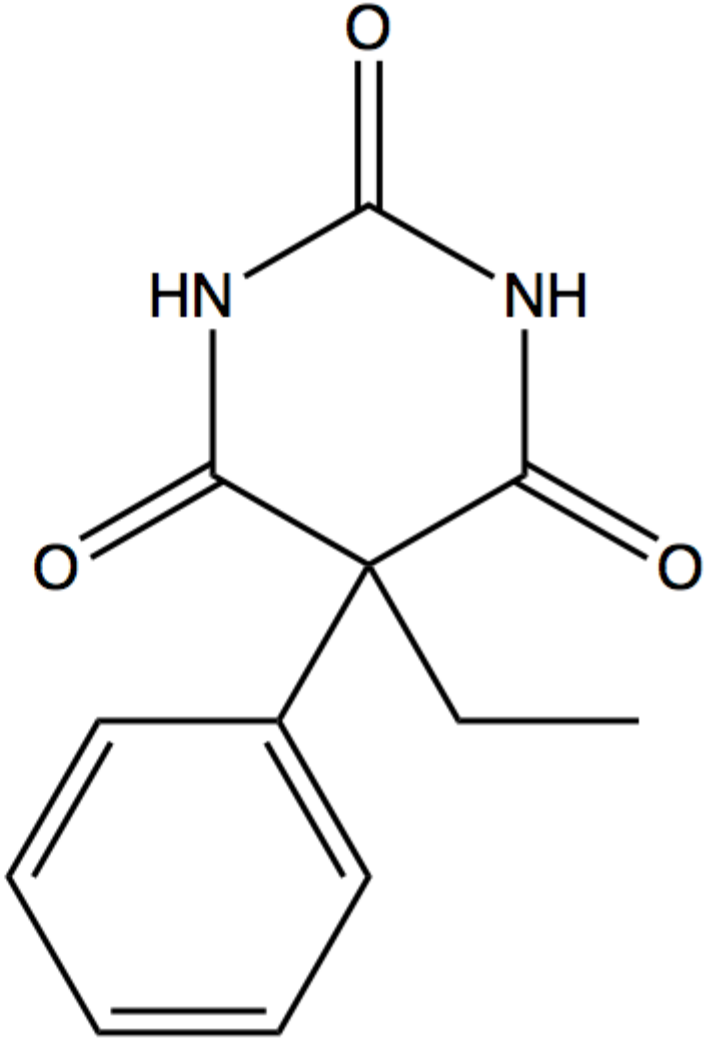


Barbiturate ion



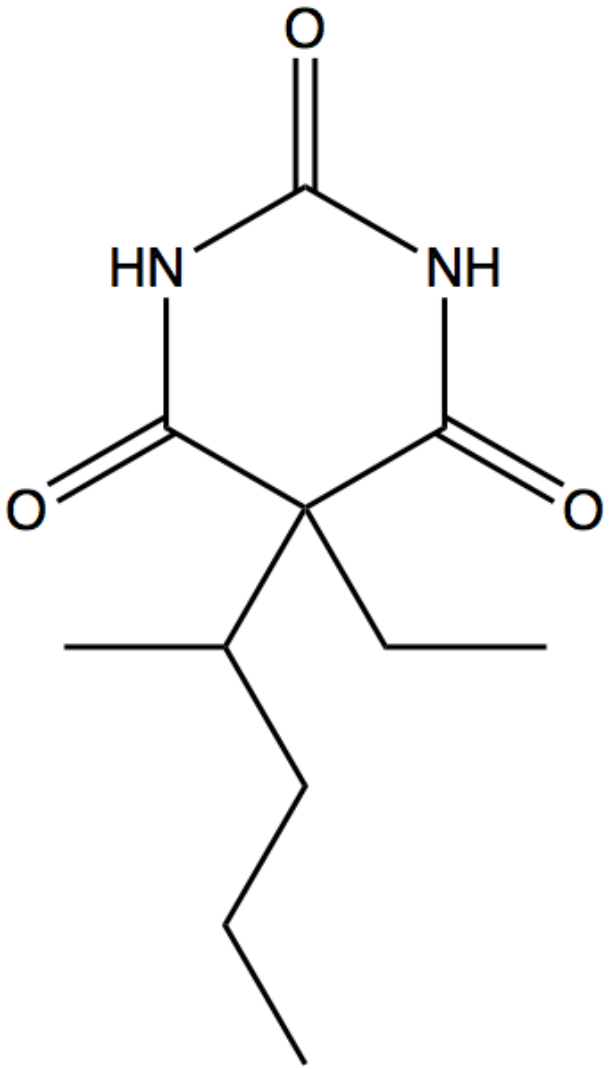
Barbital

1904 - First barbiturate



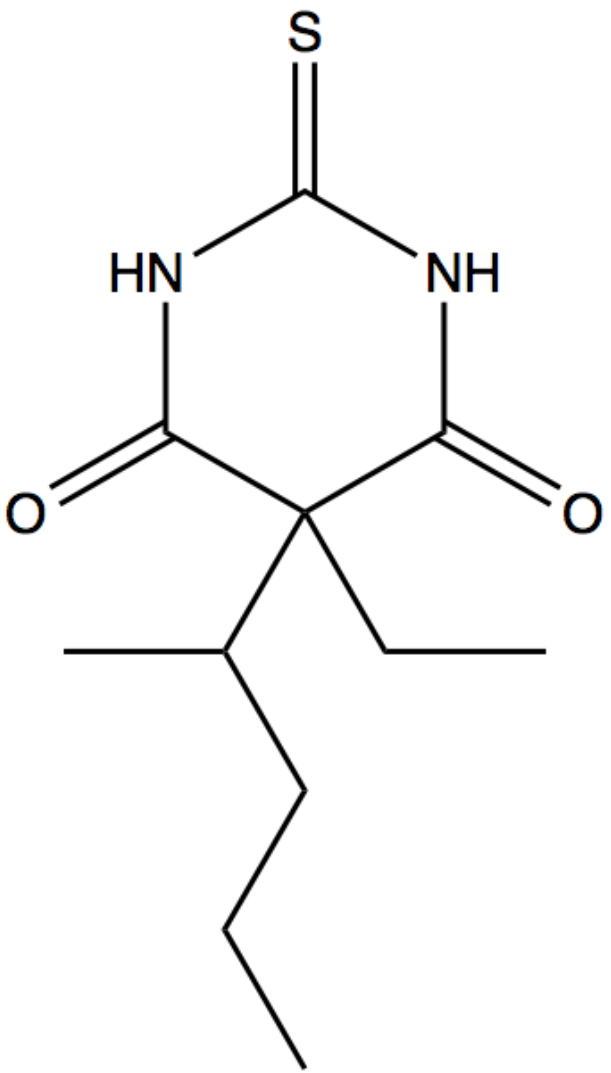
Phenobarbital

1912 - Most important



Pentobarbital

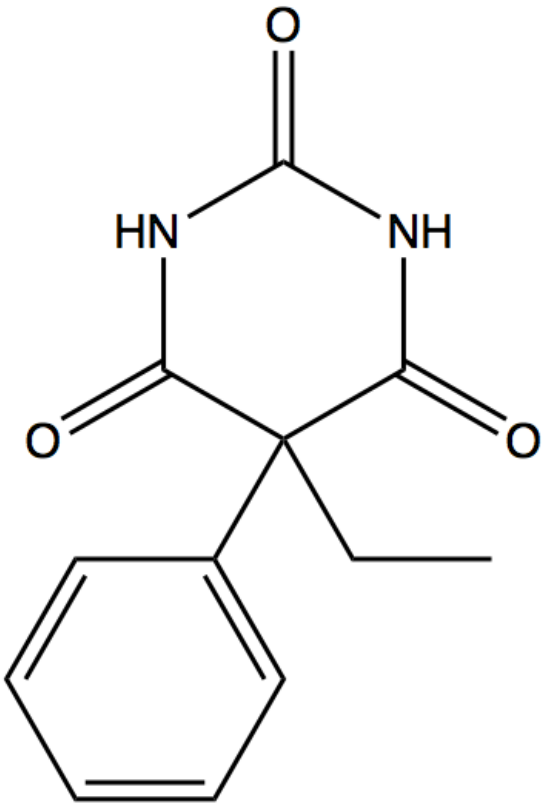
1930 - Most like alcohol



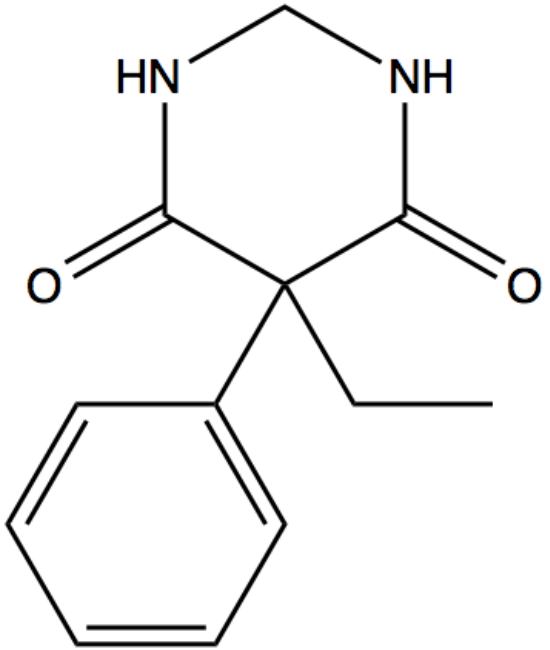
Thiopental

1935 - IV anesthetic

"Truth serum"



Phenobarbital

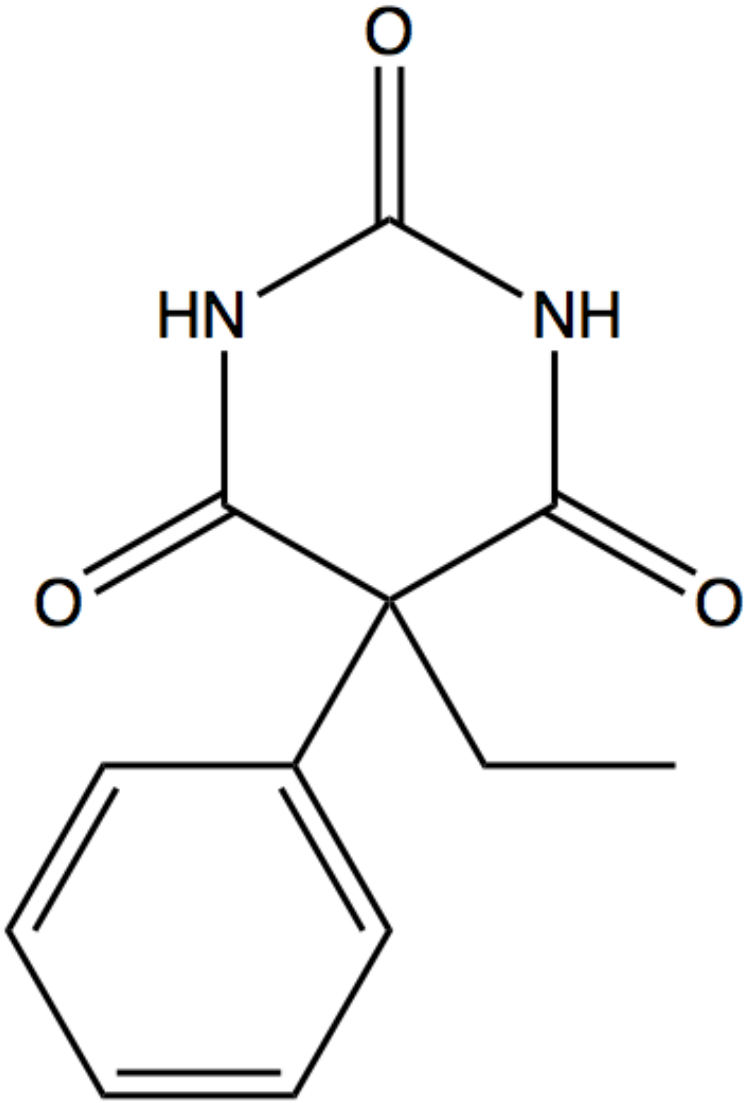


Primidone

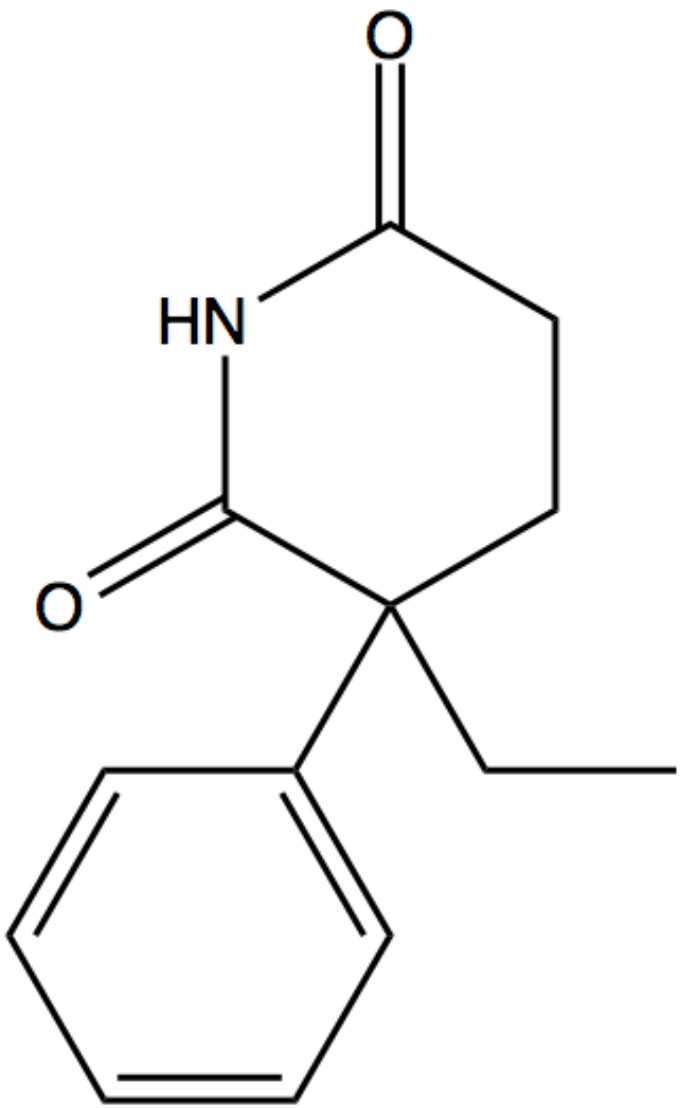
1949 – Primidone invented, advertised as a non-sedating anticonvulsant

1956 – Discovery that primidone is converted into phenobarbital in the body

1967 – Discovery that primidone and phenobarbital are identical in almost every way. Both addictive, both fatal in overdose, both similarly effective for seizures and anxiety.

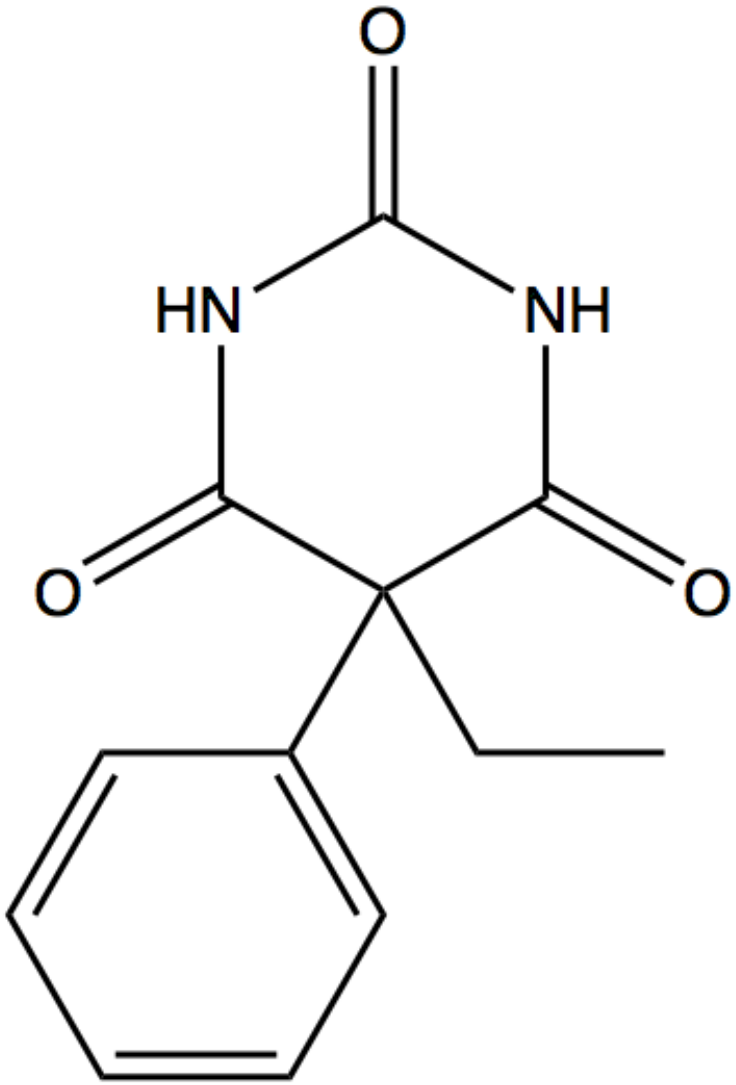


Phenobarbital

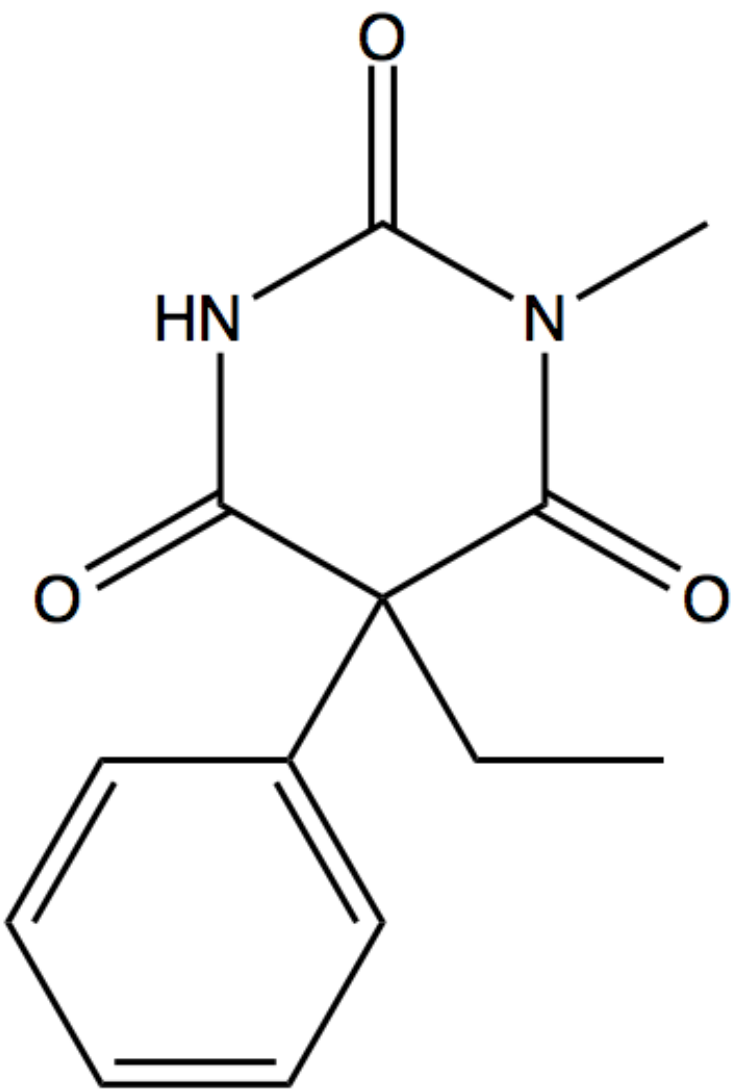


Glutethimide

1954

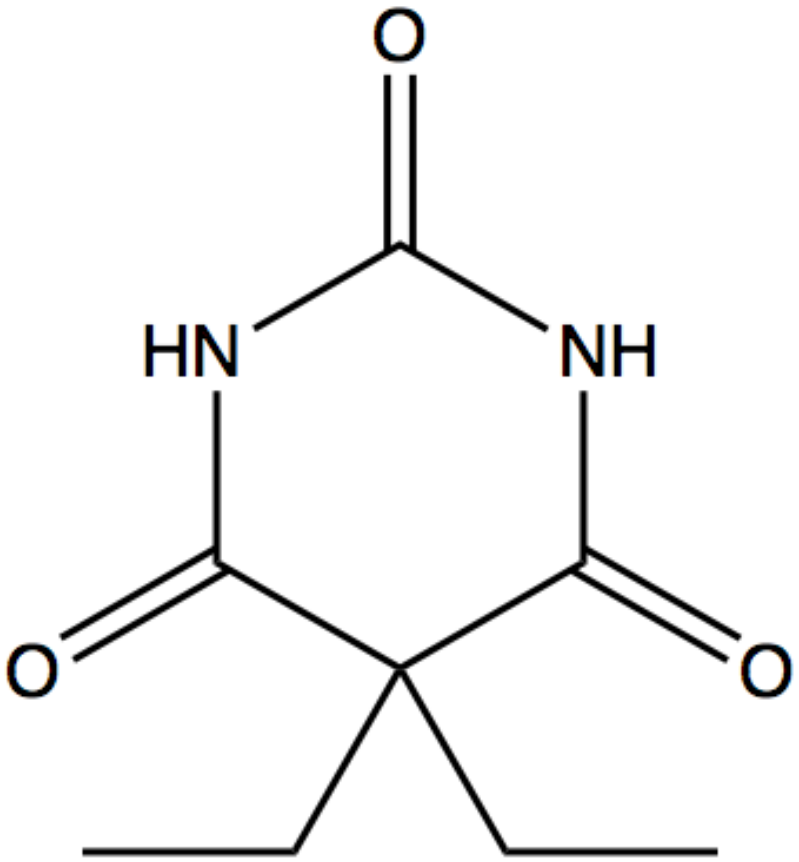


Phenobarbital

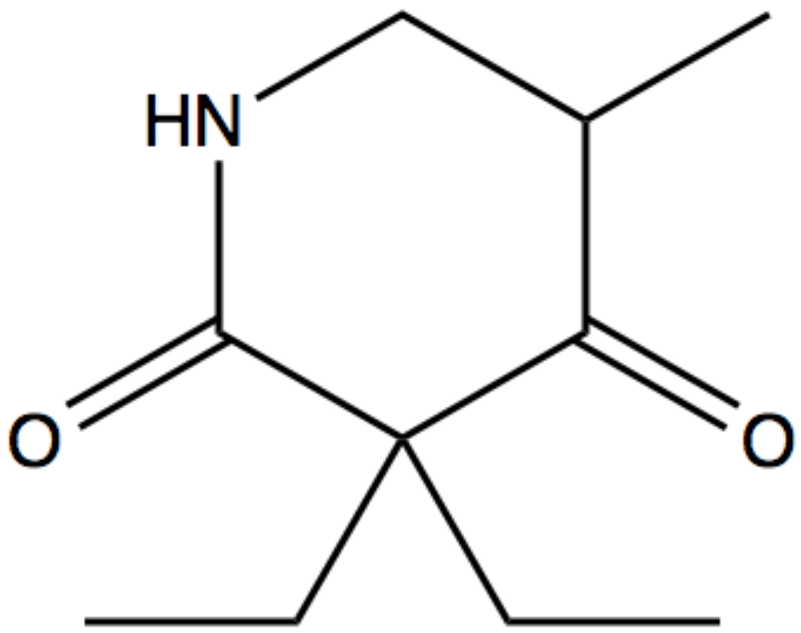


Mephobarbital

1932



Barbital
1904



Methyprylon
1955

Drug:	Normal dose:	Maximum dose:	Class:	Year:
Ethanol	3 to 5 shots (51 to 85 grams)		Pre-barb.	6000 BCE
Bromide salts	1.5 g/d	5 g/d	Pre-barb.	1857
Chloral hydrate	500 mg	1,000 mg	Pre-barb.	1869
Paraldehyde	3 mL	8 mL	Pre-barb.	1882
Barbital	600 mg	1,000 mg	Barbiturate	1904
Phenobarbital	30-100 mg	200 mg	Barbiturate	1912
Pentobarbital	100 mg	200 mg	Barbiturate	1930
Primidone	50-100 mg	200 mg	Analog	1949
Glutethimide	250 mg	500 mg	Analog	1954
Methyprylon	200 mg	400 mg	Analog	1955
Quaalude (methaqualone)	200 mg	400 mg	Other	1956
After 1960, "normal" doses were less potent				
Librium (chlordiazepoxide)	25 mg	-	Benzodiazepine	1960
Valium (diazepam)	10 mg	40 mg/d	Benzodiazepine	1963
Klonopin (clonazepam)	0.5 mg	-	Benzodiazepine	1971

Sleep Cures

Popular in the 1930's

Administer IV barbiturates, induce a coma

In average protocols you sleep about 15 days, and you are groggy for several days afterward

Motivation: Maybe brain cells need rest. This was also the motivation for insulin comas.

Mortality rate was 5 to 15%

Used for: Schizophrenia, bipolar disorder (mania), autism

Sleeping Beauty Diet

If you are sleeping, then you aren't eating

Never widely popular, always regarded as deeply irresponsible and dangerous

Used by **Elvis Presley**

Barbiturate Popularity

From 1945 to 1960, enough barbiturates were produced in the US to put 10% of the population to sleep every single night. The equivalent of 100 mg of pentobarbital per night, for 15 million people.

From the invention of barbital (1904) to about 1955, barbiturates were generally the most prescribed drugs in America (and other countries). In the late 1950's they were replaced by **meprobamate (Miltown)**, another sedative (cf. Jerry Lettvin).

Barbiturate Overdose

You stop breathing

Sometimes you choke on vomit

Famous victims:

- Josef von Mering (maybe)
- H. Emil Fischer (suicide) (maybe)
- Marilyn Monroe (suicide)
- Jimi Hendrix (choked on vomit)
- Judy Garland (*The Wizard of Oz*)

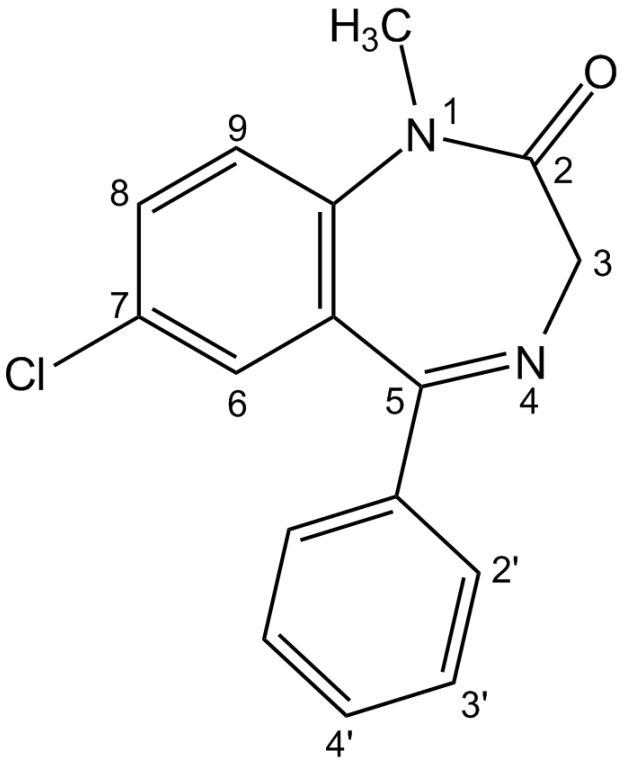
Benzodiazepine Popularity

1960 – **Librium** is released and immediately steals a lot of the sedative market share

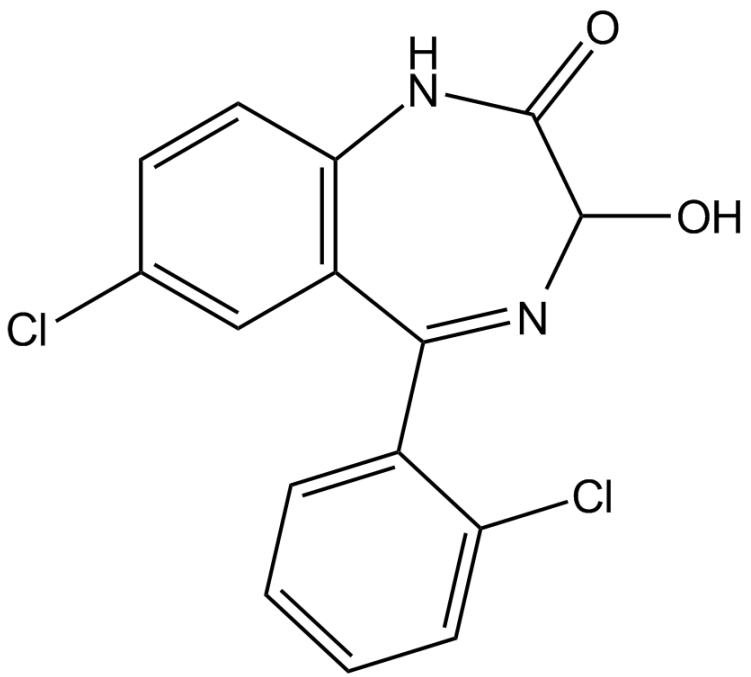
1963 – **Valium** is released

From 1969 to 1982, Valium was the most prescribed drug in the US.

Benzodiazepine receptor ligands



Diazepam



Lorazepam

Full agonists

Benzodiazepine receptor ligands

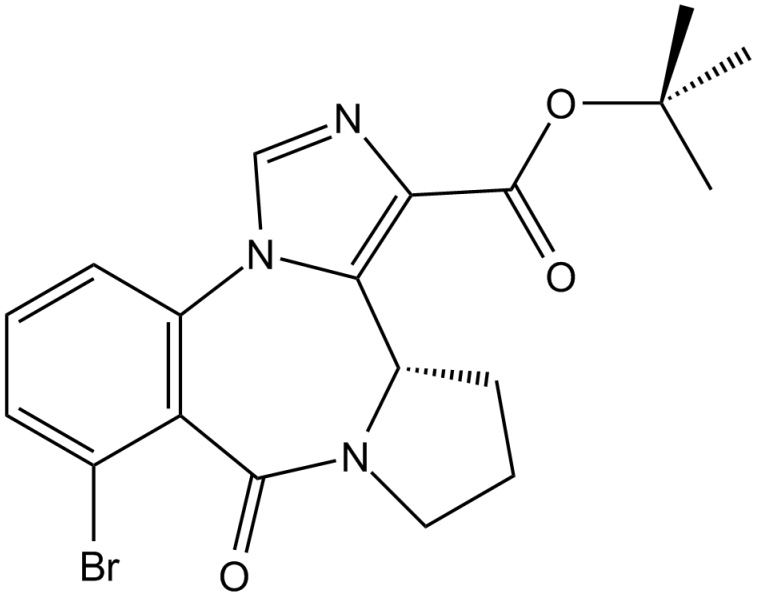


Figure 5: Bretazenil, a partial agonist

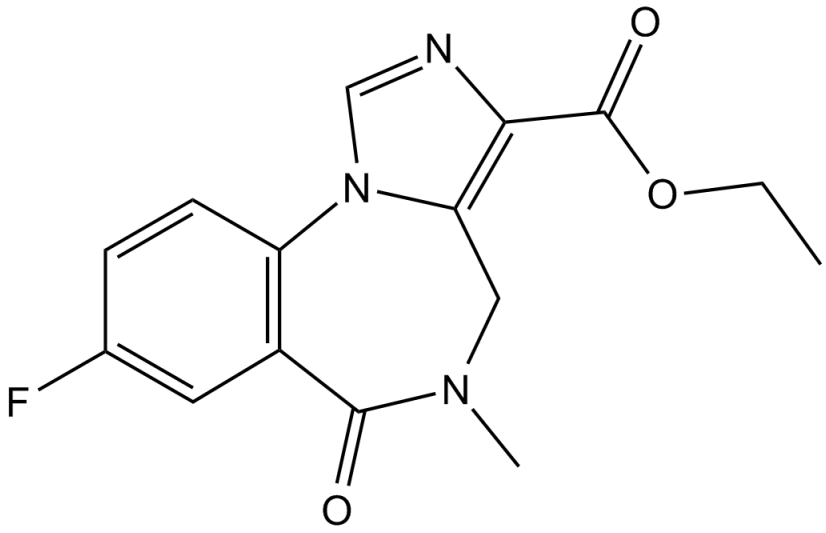


Figure 6: Flumazenil, an antagonist

Benzodiazepine receptor ligands

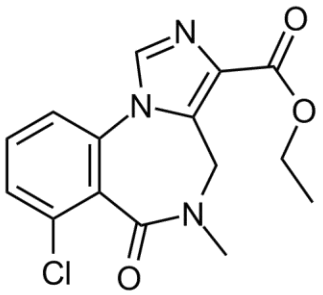


Figure 7: Sarmazenil, Ro 15-3505

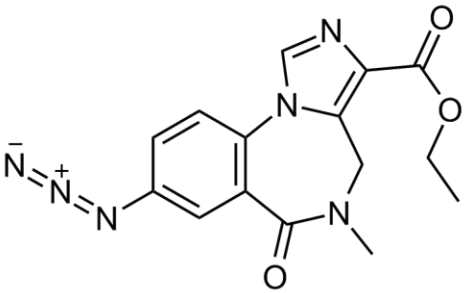


Figure 8: Ro 15-4513

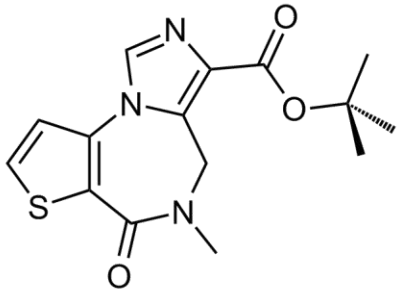
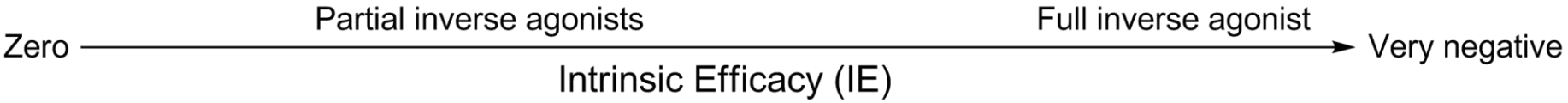
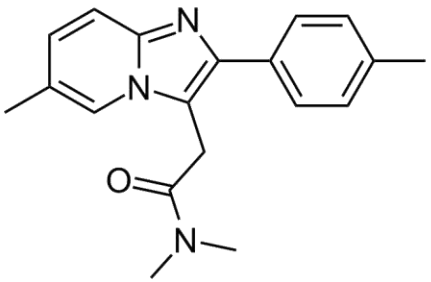


Figure 9: Ro 19-4603

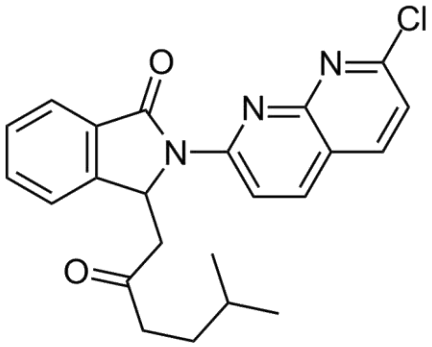


Inverse agonists

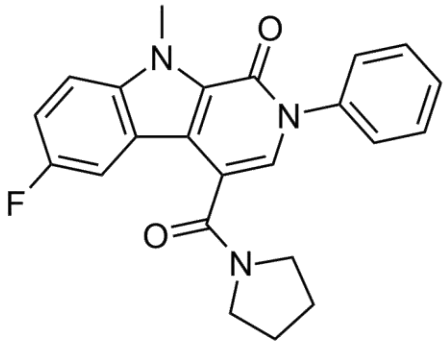
Benzodiazepine receptor ligands



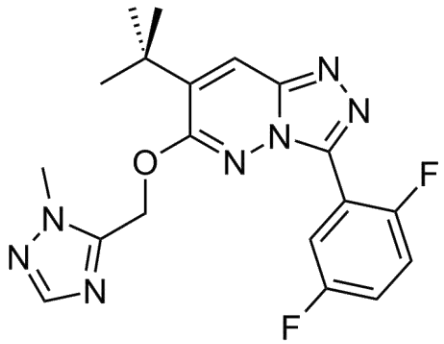
8.1: Zolpidem



8.2: Pagoclone



8.3: SL 651498



8.4: L-838417

α_1	+++	+	+	Antag.
α_2	0	+++	+++	++
α_3	0	+?	++	++
α_5	0	+?	+?	++

Selective agonists

ES.S10 Drugs and the Brain

Spring 2013