THE NORTHERN HOSPITAL

PREGABALIN

"Then we came forth, to see the stars again"
Gustave Dore, woodcut print 1865

"Here it is morning when it is evening there,
and the one whose hair provided us a ladder
is fixed exactly as he was before.

"It was on this side that he fell from Heaven.
And the dry land that used to stand above,
in fear of him immersed itself in water

"and fled into our hemisphere. And perhaps
to escape from him the land we'll find above
created this lacuna when it rushed back up".

As far as one can get from Beelzebub,
in the remotest corner of this cavern,
there is a place one cannot find by sight,

but by the sound of a narrow stream that trickles
through a channel it has cut into the rock
in its meanderings, making a gentle slope.

Into that hidden passage my guide and I
entered, to find again the world of light,
and, without thinking of a moment's rest,

we climbed up, he first and I behind him,
far enough to see, through a round opening,
a few of those fair things the heavens bear.
Then we came forth, to see again the stars.

Closing lines of The Inferno, Canto XXXIV 126-139,
Dante Alighieri (1306-1317)

At the end of their long terrifying journey through Hell, Virgil and Dante find themselves within the frozen floor of the Tenth Circle at the feet of Satan himself. Their journey has come to an end, but now they must find a way out. Virgil knows that there is only one way out - they must feel their way in the darkness to a hidden crevice in the rocks, where the river Lethe runs down from the surface of the Earth into Hell. The river carries the sins, now forgotten, of those amoung the living far above, who have purged themselves of them. Virgil finds the crevice and they are able to follow the river back to the surface. They emerge from their horrifying ordeal to once again see the stars of the cool night.

When we prescribe pregabalin, we need keep in mind, that like the Tenth circle of Hell, there is only one way out! Once administered, for pregabalin there is only one way out - the renal tract!

PREGABALIN

Introduction

Pregabalin (trade name in Australia, "**Lyrica**") is an analogue of **gamma-aminobutyric acid (GABA)** and is structurally related to gabapentin.

It was designed as a more potent successor to gabapentin.

Like gabapentin it has two *principle* indications:

1 An **anticonvulsant** agent

2 An **analgesic**:

- Particularly in regard to **neuropathic pain**.

See also separate documents on:

- **Gabapentinoid Toxicity (in Toxicology folder).**
- **Neuropathic Pain (in Clinical Presentations folder).**

History

Pregabalin was synthesized in 1990 as an anticonvulsant, by medicinal chemist **Richard Bruce Silverman** at Northwestern University in Evanston, Illinois.

It was approved for clinical use by the European Union and the FDA in 2004.

Pregabalin was introduced into clinical practice in Australia in 2005, approved for epilepsy and neuropathic pain.

In March 2013, it was subsidized on the Pharmaceutical Benefits Scheme (PBS) for neuropathic pain not responsive to other treatments. Since that time its prescription has soared, as has reports of its adverse effects.

Chemistry

Pregabalin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid**)**

Gabapentinoids, also known as **$\alpha_2\delta$ ligands**, are a class of drugs that are derivatives of the inhibitory neurotransmitter γ-aminobutyric acid (GABA)

Gabapentinoids include:

1. Gabapentin

2. **Pregabalin**

Classification

There is no general consensus on the classification of anticonvulsant drugs, in part due to the wide structural variation as well as the wide variation in the mechanisms of actions of these agents.

The precise mechanisms of action of the non-barbiturate and non-benzodiazepines agents are imperfectly understood.

Many agents probably have more than one action, and individual specific actions can overlap between agents.

In the broadest terms modern anticonvulsant agents can be divided into the barbiturates, the benzodiazepines and other agents.

1. Barbiturates:

   The principally used agents are:

   - Phenobarbitone
   - Primidone

2. Benzodiazepines:

   The principally used agents are:

   - Diazepam
   - Midazolam
   - Clonazepam

3. Other antiepileptics:

   These agents include:

   - Carbamazepine
   - Ethosuximide
   - Gabapentin
   - Lacosamide
   - Perampanel
   - **Pregabalin**
   - Sulthiame
   - Tiagabine

- Lamotrigine
- Levetiracetam
- Oxcarbazepine
- Phenytoin
- Topiramate
- Valproate
- Vigabatrin
- Zonisamide

Preparation

Pregabalin as:

Capsules:

- **25 mg, 75 mg, 150 mg, 300 mg.**

Mechanism of Action

Although a structural analogue of **GABA**, the precise mechanism of action of pregabalin is unclear.

Pregabalin does *not* show affinity for receptor sites of several common drugs that are used for treating seizures or pain. [3]

- It does not interact with either $GABA_A$ or $GABA_B$ receptors.
- It is not converted metabolically into GABA or another GABA agonist.
- It is not an inhibitor of acute GABA uptake or degradation.

Postulated mechanisms of action include a reduction in calcium influx at nerve terminals by blocking the alpha 2-delta subunit of voltage-dependent calcium channels. This is thought to inhibit the release of excitatory neurotransmitters in the dorsal horn of the spinal cord, reducing glutamate availability at NMDA and non-NMDA receptors.

Pharmacodynamics

Clinical effects include:

1. Anticonvulsant activity
2. Analgesic activity for **neuropathic** pain.
3. Anxiolysis

Pharmacokinetics

Absorption:

- Pregabalin is given orally.

  It is rapidly absorbed, with peak plasma concentrations occurring within 1 hour

- Pregabalin oral bioavailability is estimated to be greater than or equal to 90 % and is independent of dose.

Distribution:

- The Vd 0.56 L/kg.
- Pregabalin is *not* bound to plasma proteins.
- Pregabalin has been shown to cross the blood brain barrier
- It is not known if pregabalin crosses the human placenta.
- Pregabalin is distributed into human breast milk.

Metabolism and excretion: [2]

- Pregabalin, (like gabapentin) does not undergo hepatic metabolism, (to any significant degree).
- Pregabalin (like gabapentin) is eliminated primarily by renal excretion as unchanged drug.

  Pregabalin plasma clearance and renal clearance are directly proportional to creatinine clearance

- The elimination half-life is around 6.3 hours.

Indications

Principle indications include:

1. Analgesia:

   Particularly for **neuropathic pain** such as:

   - Diabetic neuropathy
   - Post-herpetic neuralgia
   - Complex regional pain syndromes
   - Trigeminal neuralgia

Pregabalin is commonly prescribed for sciatica, however in any given individual it is difficult to ascertain with certainty the relative contributions of nociceptive pain (for which it would be expected that pregabalin would not be effective) and neuropathic pain (for which it would be expected that pregabalin could be effective).

The role of pregabalin in sciatica has been trialed, however no clear benefit was found. [5]

2. Anticonvulsant:

    - **Partial (focal) seizures**, with or without secondary generalization, which are not controlled satisfactorily by other antiepileptic drugs, initially as adjunctive treatment. [2]

Less common indications include:

3. Generalized anxiety disorder.

Contraindications/ Precautions

1. Renal impairment.

    - Doses should be reduced.

2. Pregabalin may be synergistic with alcohol and other CNS depressants with respect to sedation.

3. Known hypersensitivity to pregabalin

4. Caution should be exercised when prescribing gabapentinoids for people with a history of psychiatric problems, as significant psychiatric side effects are possible, including mood changes, new or increased depression and anxiety, and new onset suicidal ideation and behaviour.

Pregnancy:

Pregabalin is a class B3 drug with respect to pregnancy

Class B3 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

There is limited information available describing the use of pregabalin during pregnancy. One study has suggested pregabalin monotherapy is not associated with an increased risk of congenital malformations.

However, combination with other antiepileptic agents may be associated with an increased risk of congenital malformations.

The decision to treat should be made on an individual basis by considering the risks and benefits to both mother and fetus. Consider an alternative treatment during pregnancy if possible. Consultation with a neurologist for further advice is recommended.

Women treated with pregabalin for neuropathic pain should be referred to a pain specialist for further advice during pregnancy.

Breast feeding:

There is limited information available following the use of pregabalin during breastfeeding.

An abstract has reported extensive passage of pregabalin into breast milk, but low concentrations have been measured and no adverse effects were noted in the breastfed infant.

Women who choose to breastfeed their healthy full-term infant while taking pregabalin should observe the infant for adverse effects such as irritability, poor feeding and excessive drowsiness.

Adverse Effects

These may include:

1. Sedation
2. Visual disturbance (including blurred vision, diplopia)
3. Ataxia
4. Dysarthria
5. Memory impairment
6. Insomnia
7. Mood changes:
    - Euphoria (abuse potential)
    - Depression

8. Peripheral edema

Abuse potential:

Pre-marketing studies suggested that pregabalin had a low abuse potential, but despite this, there have been numerous reports of misuse and abuse.

The following have been reported

1. Euphoria

    - Drug users take increasingly larger doses of pregabalin to achieve euphoric and dissociative effects

2. Tolerance

3. Withdrawal

Withdrawal symptoms more likely when high doses are stopped abruptly.

Dosing

For adults:

- **Pregabalin 75 mg orally, daily.**

- **Increase to twice daily after 2 or 3 days and then more slowly up to 300 mg twice daily**

Note that failure to respond to either pregabalin or gabapentin does not predict failure to respond to the other drug; the tolerability and efficacy of the two drugs may be different in individual patients. [1]

Avoid stopping pregabalin abruptly (as this may cause anxiety, insomnia, headache, sweating, nausea and diarrhoea)

Reduce doses gradually over at least a week.

References

1. eTG - September 2019.

2. Pregabalin in Australian Medicines Handbook, Accessed September 2014.

3. Pregabalin in MIMs 1 August 2104.

4. Pregabalin in RWH Pregnancy & Breastfeeding Guidelines, November 2018.

5. Stephanie Mathieson at al. Trial of Pregabalin for Acute and Chronic Sciatica. NEJM 2017; 376:1111-20.

    - DOI: 10.1056/NEJMoa1614292

Dr J. Hayes

Acknowledgments:
Dr Tom Brough
Reviewed September 2019