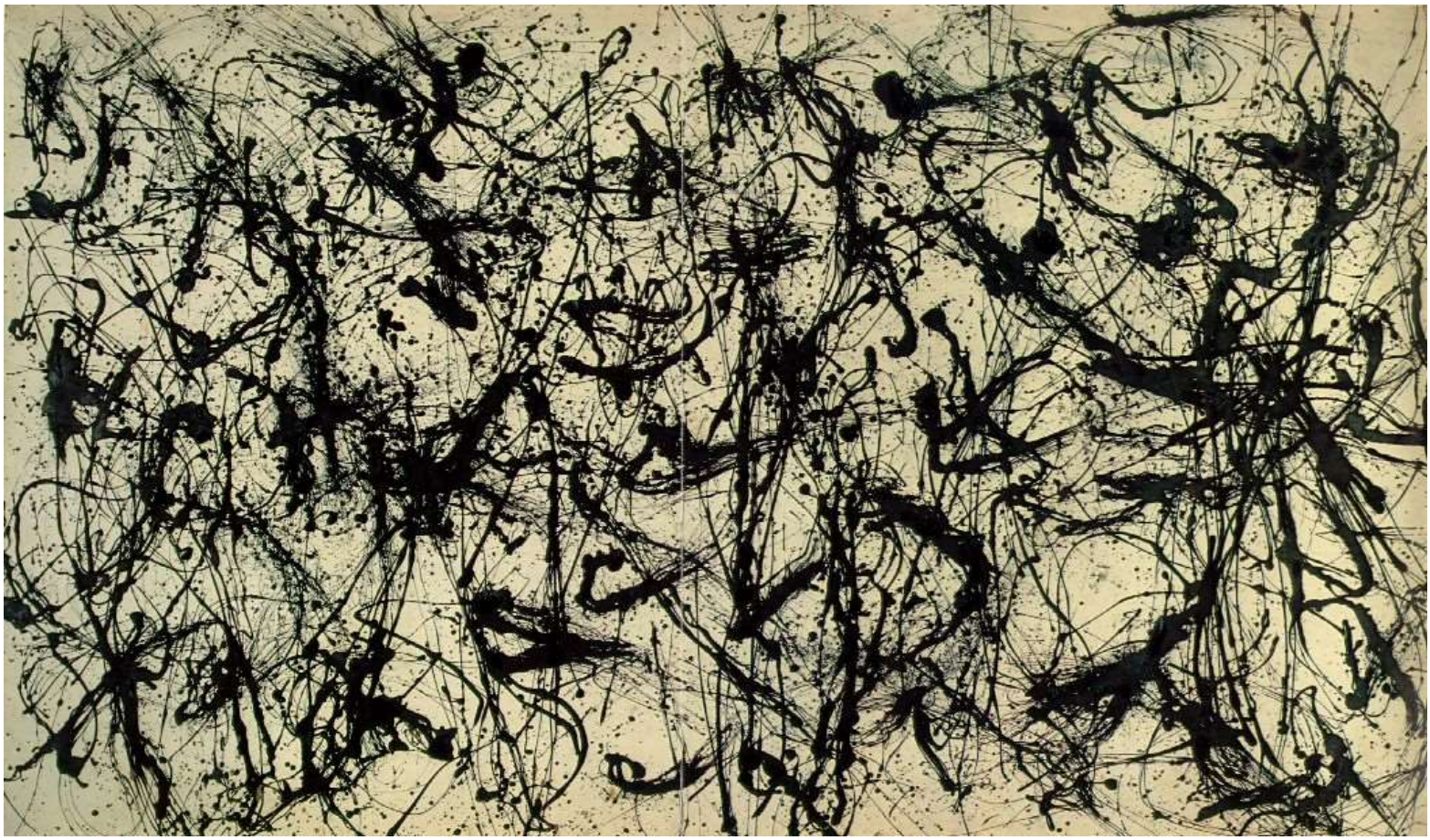
THE NORTHERN HOSPITAL

GABAPENTIN



Number 32 1950, enamel on canvas, Jackson Pollock.

Why did Jackson Pollock begin to drip paint? What was the source of his inspiration? The question has preoccupied artists, critics, and Art historians since the drip paintings first appeared in 1947; stories of his "discovery" are legion....

It was a simple gesture. In on hand he held a can of oil paint, thinned to the consistency of honey. In the other, a stick - probably the one he used to mix the paint with turpentine. On his knees beside a small canvas, he dipped the long stick in the can of paint then waved it over the canvas. From the end of the stick, held at a downward angle, a fine line of paint dribbled onto the canvas below. It formed a tint stream. As the paint on the stick ran out, the line thinned, then choked into drops. He repeated the gesture. Each time, he learned something new: if he slowed his movement, the stream would puddle; speed up and it narrowed; move closer to the canvas and it smoothed; farther away and it rippled. Pass followed pass. The strands began to overlap and interweave. A sweep of his arm produced a rough circle while a flick of the wrist launched an extravagant ellipse. By

adding more thinner to the paint, he could fling the line even farther. He learned about tools; a still brush held more paint than a stick, a full circuit or two, but it always threatened to flood the line. When he shook it, the stream turned to rain. That, too, he could control by thinning the paint, loading less paint on the brush, or holding the brush higher above the canvas. A stick required more reloadings but produced a finer, more consistent line and, when the paint was especially thin, a dew-like wash. Each discovery was woven into a densensing web....

With only a broad house painting brush and a bucket of black enamel, he hurled himself at a 8' 10" by 15' expanse of unsized, unforgiving canvas. Instead of sprays and filigrees, he poured great ropes black as thick as fists, winding them into dense knots, then out again, across the stark white field to form new knots. Instead of working from one small area to the next, he roamed over the canvas all at once, his arm sweeping behind him as he giant-stepped from one side to the other. On his knees, arm outstretched toward the center, hands black to the wrists, he unfurled thick ribbons of paint in a single gesture, tipping the can of paint as he passed to quicken or slow the flow. The lines rose and fell, twisted and coiled, dividing like arteries or ending abruptly in bursts of black. Where there had been delicate webs, he wound dense, taut, capillary tangles; where there had been pastel clouds, he flooded the line with turbulent pools; even the droplets, flung from a heavily laden brush, fell full, round, and final on the canvas, each one distinct from across the room. This was the calligraphy of arrogance. Not since the Guggenheim mural had he worked so quickly or so confidently, combining - in what became known as Number 32 1950 - the calligraphic nuance of earlier, smaller works like Number 23 1949 and Number 26 1949, works that explored the drip technique in blown -up detail, with the bravura compositional control of complex paintings like Number 1 1948.

Finally, the vision matched the scale.

Steven Naifeh and Gregory White Smith, Jackson Pollock,
An American Saga 1989, Pulitzer Prize 1991.

The reasons for Jackson Pollock's "drip paintings", and how these came about in the late 1940s and early 1950s, remains a complete enigma - as do their meanings. Theories are interesting, some quite fascinating and certainly they are legion. According to Jackson himself, after some pause for thought, he called his drip paintings simply "memories....arrested in space"....a haunting image indeed!

Perhaps the seemingly "random" movements reflected the thoughts surging through his mind at the time - we do know that his drip paintings were precisely controlled productions - the line, the intensity, the ebb and the flow - though working quickly, all movements were deliberately and very accurately controlled. Jackson Pollock's drip paintings certainly have the cadence of a pulsing organic entity - arteries and veins perhaps - but perhaps even more so one sees the very neural networks of his mind - perhaps they are indeed his very memories arrested not only in space ...but also in time!

Just as the miraculous inner workings of the mind remain as obscure to us as a Jackson Pollock drip painting, so too are the inner workings of many of the drugs we use to supposedly control it !- Gabapentin being a case in point!

GABAPENTIN

Introduction

Gabapentin (trade name "**Neurontin**". Amoung others) is an analogue of **gamma-aminobutyric acid (GABA).**

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

Gabapentin was first approved for clinical use in the US in 1993.

Chemistry

Gabapentin 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
   - Lamotrigine
   - Levetiracetam
   - Oxcarbazepine
   - Phenytoin
   - Perampanel
   - Pregabalin
   - Sulthiame
   - Tiagabine
   - Topiramate
   - Valproate
   - Vigabatrin
   - Zonisamide

Preparation

Gabapentin as:

Tablets:

- **600 mg, 800 mg.**

Capsules:

- **100mg, 300 mg, 400 mg.**

Mechanism of Action

Although gabapentin is *structurally related* to the neurotransmitter GABA (gamma-aminobutyric acid) - its exact mechanism of action as an anticonvulsant and analgesic is unknown.

Its mechanism of action appears to be different from that of several other drugs that interact with GABA synapses, including valproate, barbiturates, benzodiazepines, GABA transaminase inhibitors, GABA uptake inhibitors, GABA agonists and GABA prodrugs. [3]

It does not appear to bind to $GABA_A$, $GABA_B$, glutamate, glycine or N-methyl-d aspartate (NMDA) receptors.

It does not interact with sodium channels *in vitro* and so also differs from phenytoin and carbamazepine.

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.

Pharmacokinetics

Absorption:

- Gabapentin is given orally.

  It is absorbed by a **saturable** amino acid uptake system in the gastrointestinal tract, so that as the dose is increased, the bioavailability decreases.

  For example there is 60% absorption from a 300 mg dose, but only 40% absorption from a 900 mg dose. [1]

  Capsule formulations can be opened and the contents mixed with 10 mls of water for administration via a NG tube.

Distribution:

- Gabapentin does not bind to plasma proteins.

- Gabapentin can cross the human placenta
- Gabapentin is distributed into human breast milk in small amounts.

Metabolism and excretion: [2]

- Gabapentin is **not** metabolized in the human liver (to any significant extent).
- It is excreted unchanged in the urine.
- The elimination half-life of gabapentin is 5 -7 hours and is unaltered by dose or following multiple dosing.
- Gabapentin elimination is rate constant, plasma clearance and renal clearance are directly proportional to creatinine clearance.
- In elderly patients and in patients with impaired renal function, gabapentin plasma clearance is reduced.

Indications

1. Analgesia:

   Particularly for **neuropathic pain** such as:

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

2. Anticonvulsant:

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

Contraindications/ Precautions

1. Renal impairment

   - The dose must be reduced in cases of renal impairment.

2. Absence seizures:

- There is a risk of aggravation of this type of seizure activity.

3. Gabapentin may be synergistic with alcohol and other CNS depressants with respect to sedation.

4. Known hypersensitivity to gabapentin

5. 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:

Gabapentin is categorized as a class B1 drug with respect to pregnancy.

Class B1 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 not shown evidence of an increased occurrence of fetal damage.

From the very limited information available, gabapentin use in early pregnancy has not been associated with an increased risk of birth defects.

However, a single case report has described signs of withdrawal in the neonate following prolonged in utero exposure to gabapentin, baclofen and oxybutynin.

The decision to treat should be made on an individual basis by considering the risks and benefits to both mother and fetus.

Combination with other antiepileptic agents may be associated with an increased risk of congenital malformations.

Consultation with a neurologist for further advice is recommended.

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

If gabapentin is the treatment of choice during pregnancy, use the lowest effective dose for the shortest duration possible.

Breast feeding:

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

Small amounts of gabapentin are excreted into breast milk, but these amounts are unlikely to pose harm to the breastfed infant.

Women who choose to breastfeed their healthy full-term infant while taking gabapentin should use the lowest effective daily dose and observe the breastfed infant for potential adverse effects such as excessive drowsiness, poor feeding and restlessness.

Adverse Effects

These may include:

1. Sedation

2. Amnesia

3. Confusion/ psychosis (uncommon).

4. Nystagmus

5. Ataxia

7. Mood changes:

    - Euphoria (abuse potential)

    - Depression

7. Hypersensitivity skin reactions, (which can be severe).

Dosing

For adults: [2]

Partial (focal) seizures:

- 300 mg on the first day at bedtime.

- Increase by 300 mg daily up to 0.9 - 1.8 grams daily in 3 doses (up to 3.6 grams daily in some patients).

Neuropathic pain:

- Initially 100 - 300 mg at night.

- Increase dose gradually every 3 - 7 days according to response; usual range 1.8 - 3.6 grams daily in 3 doses.

Doses should be reduced in renal impairment.

Avoid stopping gabapentin *abruptly* (as this may result in anxiety, insomnia, nausea, pain and sweating).

When gabapentin is used as an anticonvulsant, abrupt withdrawal may precipitate seizures.

The dose should be gradually reduced over at least a week

Jackson Pollock drip painting, Silver gelatine photograph, 1950, Hans Namuth.

References

1. eTG - September 2019.

2. Gabapentin in Australian Medicines Handbook, Accessed August 2014.

3. Gabapentin in MIMs 1 December 2013

4. Gabapentin in RWH Pregnancy & Breastfeeding Guidelines, 31 October 2018.

Dr J. Hayes.
Reviewed September 2019.