

**VENLAFAXINE**



*“The Wanderer above the Sea of Fog”, oil on canvas, 1818, Caspar David Friedrich.*

*One night as the rain fell in torrents, Humboldt lay in his hammock fasted to a palm tree in the jungle. The lianas and climbing plants formed a protective shield high above him. He looked up into what seemed like a natural trellis decorated with the long dangling orange blossoms of heliconias and other strangely shaped flowers. Their camp-lit fire lit up this natural vault, the light of the flames licking the palm trunks up to sixty feet high. The blossoms whirled in and out of these flickering illuminations, while the white smoke of the fire spiraled into the sky which remained invisible behind the foliage.*

*He had described the rapids of the Oronico which were “illuminated by the rays of the setting sun” as if a river made of mist were “suspended over its bed”. Though he always measured and recorded, Humboldt also wrote of how “coloured bows shine, vanish and reappear” at the great rapids and of the moon “encircled with coloured rings”. Later he delighted in the dark river surface which during the day reflected like a perfect mirror the blossom-loaded plants of the riverbanks, and at night the southern star constellations. No scientist had referred to nature like this before. “What speaks to the soul”, Humboldt said, “escapes our measurements”. This was not nature as a mechanistic system but a thrilling new world filled with wonder. Seeing South America with the eyes that Goethe had given him, Humboldt was enraptured....*

*Wordsworth’s friend and fellow poet Coleridge found Humboldt’s work equally stimulating. Coleridge had probably first been introduced to Humboldt’s ideas at Wilhelm and Caroline von Humboldt’s house in Rome, where he had spent time in late 1805. He had met Wilhelm - the brother of the “great traveler”, as Coleridge described him - shortly after his arrival. The salon at the Humboldt’s had been alive with Alexander’s tales from South America but also with discussions of his new concept of nature. Back in England, Coleridge began to read Humboldt’s books and copied sections into his notebooks, returning to them when thinking about science and philosophy because he was grappling with similar ideas.*

*Both Wordsworth and Coleridge were “walking poets” who not only needed to be out in nature but also wrote outdoors. Like Humboldt, who insisted that scientists had to leave their laboratories to truly understand nature, Wordsworth and Coleridge believed that poets had to open the doors of their studies and walk through meadows, over hills and besides rivers. An uneven path, or tangled woods were Coleridge’s preferred places to compose, he claimed. A friend estimated that Wordsworth, by the time he was in his sixties, had covered around 180,000 miles. They were part of nature, searching for the unity within but also between man and his environment.*

*Like Humboldt, Coleridge admired Immanuel Kant’s philosophy - “a truly great man” as he called him - and enthused initially about Schelling’s “Naturphilosophie” for its search of unity between the Self and Nature - the internal and the external world. It was Schelling’s belief in the role of the creative “I” in the understanding of nature that resonated with Coleridge. Science needed to be infused with imagination or, as Schelling said, they had “to give once again wings to physics”.*

*Fluent in German, Coleridge had for long been immersed in German literature and science. He had even suggested a translation of Goethe’s masterpiece “Faust” to Humboldt’s publisher, John Murray. More than any other contemporary play, “Faust”*

*addressed issues that occupied Coleridge intensely. Heinrich Faust saw how everything hung together. "How it all lives and moves and weaves into a whole! Each part gives and receives". Faust declares in the first scene, a sentence that could have been written by either Humboldt or Coleridge.*

*Coleridge was lamenting the loss of what he called the "connective powers of the understanding". They lived in an "epoch of division and separation", of fragmentation and the loss of unity. The problem, he insisted, lay with philosophers and scientists such as Rene Descartes or Carl Linnaeus, who had turned the understanding of nature into a narrow practice of collecting, classification or mathematical abstraction. This "philosophy of mechanism", Coleridge wrote to Wordsworth, "strikes Death". It was the naturalist with his urge to classify, Wordsworth agreed, who was a "fingering slave - one who would peep and botanize - upon his mother's grave?'. Coleridge and Wordsworth were turning against the idea of extorting knowledge from nature with "screws or levers" - in Faust's words - and against the idea of a Newtonian universe made up of inert atoms that followed natural laws like automata. Instead they saw nature as Humboldt did - dynamic, organic and thumping with life.*

*Andrea Wulf, "The Invention of Nature: Alexander von Humboldt's New World", Knopf, 2015.*

*The astonishing scientific revolution of the Seventeenth and Eighteenth centuries that would come to be known as the "Enlightenment" or the "Age of Reason", would change forever humanity's view of Universe. The new scientific method by the Nineteenth century had become firmly established and with Charles's Darwin's shocking publication of the "Origin of Species", humanity's place in the Universe became clear - at least to some. Partly as a reaction against these profoundly disturbing ideas a reactionary genre in the Arts and philosophy emerged, known as "Romanticism". The movement was powerful and extremely popular particularly in the first half of the century. Exponents such as Shelly, Keats, Coleridge, Blake, Friedrich, Byron and Wordsworth were vocal in their laments of the perceived loss of spiritual meaning and values that the scientific revolution seemed to imply for people's lives. But for others the two world views were by no means incompatible. Many embraced both at one and the same time - the new scientific truths merely increasing and enhancing the wonder and awe held for "nature" and life.. The greatest and most influential of these dualists was the brilliant German polymath and Naturalist, Alexander von Humboldt. He combined the new scientific method with a style and spirit of writing that embodied the very finest sentiments of the Romantics. He was the most influential scientist in the popular mind until the time of Charles Darwin. Tragically von Humboldt died just weeks before Darwin published "The Origin of Species". knowing that he would have embraced it, it would have been profoundly fascinating to have known his opinion of the work*

*Throughout the course of the Twentieth century the vast expansion of scientific knowledge made it impossible for any one individual to be a "polymath", at least in the old sense of the word. To understand life and the Universe, reductionism became the catch cry of that century. Specialists in their fragmented and isolated fields gradually came to lose sight of the whole. This was never the case for Humboldt who saw the whole of life as an intricately related, a "web of life" as he termed it - he was the quintessential*

*Romantic scientist. The great German Romantic painter Caspar David Friedrich perhaps captured the most haunting image we could have of the widely travelled Humboldt in his depiction of the "Wanderer" who serenely purveys the awesome spectacle of nature, through both a scientific and a spiritual eye.*

*By the late Twentieth century the medical sciences had also become bogged down in radical reductionism. Though an incredibly successful approach to understanding nature on the most fundamental levels, reductionism at the same time ignored the equally important and only vaguely perceived idea of "emergence" - the phenomenon of the whole being greater than simply the sum of the parts. In the medical "science" of the field of psychiatry, reductionism held that all mental illness was merely the result of "chemical imbalances" of neurotransmitters in the brain. If one was depressed for example one merely lacked the appropriate level of various neurotransmitter in the brain. The "cure" of course was quite simply to raise the level of neurotransmitter and the symptoms would disappear. This was a an absolute boon to Big Pharma - drugs that altered brain chemistry would cure or at least control mental illness. On the back of this pseudoscience profits of cosmic dimension were made as the diagnosis of depression and anxiety massively increased to epidemic proportions.*

*But mental illness is surely a far more complex entity than a mere deficiency of serotonin or noradrenaline - indeed if this has anything at all to do with mental illness! More likely these "imbalances" - if they exists at all, and who has taken the measurements to prove it - are epiphenomenon and not a root cause. The human psyche is far more complex than that - the result of the cosmically complex interplay of eons of genetics and environment. But new "wonder drugs" continue to emerge in the treatment of psychiatric illness, just as soon as the patent expires on one agent it is replaced by the next big thing. Bromides, replaced MAOIs, which were in turn replaced by the tricyclics which were replaced again by the SSRIs. The patent on Prozac that once gripped nations is long gone and now the SNRIs are prompted as the next big thing. Agents such as venlafaxine are said to be marginally better, and promoted aggressively despite its life threatening toxicity when taken in overdose as prescribed to the most exquisitely selected population likely to overdose. Is this really progress? More likely we have simply gone full circle - tricyclics by any other name!*

*Perhaps the answer lies not in fundamentalist reductionist theories but rather to take a step back, as the Romantics and Alexander von Humboldt so urged the world to do - and like Freidrich's wanderer to look at the whole person as an integrated soul within a vast and infinitely complexly interacting "web of life".*

## **VENLAFAXINE**

### **Introduction**

**Venlafaxine** (trade name “**Effexor**”) is a potent selective **serotonin and noradrenaline** reuptake inhibitor (SNRI).

It is an **antidepressant agent** used in the treatment of **major depression**.

**The SNRIs are far more toxic in overdose than is the case with the SSRIs**

**See also separate documents on:**

- **Venlafaxine Overdose (in Toxicology folder)**
- **Serotonin Syndrome (in Toxicology folder)**

### **History**

Venlafaxine was first synthesized in the early 1980s by researchers at Wyeth Pharmaceuticals.

It was introduced into clinical practice in the United States in 1994 under the trade name Effexor.

An extended-release (XR) formulation was introduced in 1997.

### **Chemistry**

Venlafaxine is a structurally novel antidepressant; it is chemically unrelated to tricyclic, tetracyclic or the SSRI antidepressants.

### **Classification**

Antidepressants can be loosely classified into 6 groups:

#### **1. Tricyclic antidepressants (TCAs):**

TCAs inhibit the reuptake of **noradrenaline** and **serotonin** into presynaptic terminals.

*Examples include:*

- Amitriptyline
- Clomipramine
- Dothiepin

- Doxepin
- Imipramine
- Nortriptyline
- Trimipramine

2. **Monoamine oxidase inhibitors (MAOIs):**

These agents block of MAO-A and/ or MAO-B, thereby increasing the synaptic concentrations of **adrenaline, noradrenaline, dopamine** and **serotonin**.

*Examples include:*

- Phenelzine
- Tranylcypromine

3. **Selective serotonin reuptake inhibitors (SSRIs):**

The SSRIs selectively inhibit the presynaptic reuptake of **serotonin**

*Examples include:*

- Citalopram
- Dapoxetine
- Escitalopram
- Fluoxetine
- Fluvoxamine
- Paroxetine
- Sertraline

4. **Serotonin- norepinephrine reuptake inhibitors (SNRIs):**

These are **serotonin and noradrenaline** reuptake inhibitor.

*Examples include:*

- **Venlafaxine**

- Desvenlafaxine
- Duloxetine

#### 5. **Tetracyclic antidepressants:**

These have a tetracyclic chemical structure, containing four rings of atoms.

They are closely related to the tricyclic antidepressants (TCAs), which contain three rings of atoms.

*Examples include:*

- Mianserin
- Mirtazapine

#### 6. **Atypical Antidepressants:**

Essentially other newer agents not belonging to the above groups

Broadly described as atypical antidepressants, they affect serotonin, norepinephrine, and dopamine levels in varied and unique ways.

### Preparation

All current venlafaxine preparations in Australia are **controlled release** formulations:

Venlafaxine hydrochloride as:

Tablets modified (i.e extended) release formulation:

- 37.5 mg
- 75 mg
- 150 mg.

### Mechanism of Action

Venlafaxine is a potent selective **serotonin and noradrenaline** reuptake inhibitor.

Venlafaxine more potently inhibits the reuptake of serotonin compared to noradrenaline.

It weakly inhibits dopamine uptake.

It has no significant affinity for histaminergic, dopaminergic, cholinergic and adrenergic receptors. Pharmacological activity at these receptors has been hypothesised to be

associated with the various anticholinergic, sedative and cardiovascular effects seen with other psychotropic drugs.

The antidepressant action of venlafaxine in humans is believed to be associated with its potentiation of neurotransmitter activity within the central nervous system.

### Pharmacokinetics

#### Absorption:

- Venlafaxine is administered orally.

Absorption is nearly complete; however, there is significant first pass metabolism of venlafaxine in the liver which reduces the absolute bioavailability of venlafaxine to around 40 %.

- The modified release venlafaxine capsule provides a slower *rate* of absorption, compared to the immediate release formulation, but the same *extent* of absorption as the venlafaxine immediate release tablet.

#### Distribution:

- Protein binding of both venlafaxine and its active metabolite O-desmethyl-venlafaxine is approximately 30 %.
- The volume of distribution is 5-7 L/Kg.
- Venlafaxine can cross the human placenta.
- Venlafaxine is distributed into human breast milk.

#### Metabolism and excretion:

- Venlafaxine's major liver metabolite is **O-desmethyl-venlafaxine** or **desvenlafaxine**, which is an **active** metabolite.

This is also a potent inhibitor of serotonin and noradrenaline reuptake. Indeed venlafaxine and its major metabolite appear to be *equipotent* with respect to their overall action on neurotransmitter reuptake and receptor binding.

- The elimination half-life is 5 hours for **venlafaxine**

The elimination half-life is 11 hours for **desvenlafaxine**

### Pharmacodynamics

Venlafaxine may be more effective than the SSRIs, and is at least as effective as tricyclic antidepressants, in the treatment of major depression.



It should be noted however, that venlafaxine is far more **toxic in overdose** than is the case with the SSRIs.

### Indications

Indications for venlafaxine currently include: <sup>2</sup>

1. Major depression
2. Some anxiety disorders:
  - Generalized anxiety disorder
  - Panic disorder
  - Social phobia

### Contraindications/ Precautions

These include:

1. Hypersensitivity to venlafaxine.
2. CVS disease:
  - Caution in patients with hypertension / CVS disease
3. Caution with other **serotonergic** agents:
  - Coadministration with other serotonergic drugs (e.g. SNRIs, SSRIs, tramadol or triptans such as Sumatriptan, or MAOIs - selective, reversible or irreversible - within a minimum of 14 days) may result in **serotonin syndrome**.
4. Bipolar disorder: <sup>2</sup>
  - All antidepressants may provoke a manic episode when used in people with **bipolar disorder**.  
  
Some patients *without* a history of bipolar disorder may develop an antidepressant-induced manic episode; this does not necessarily imply a diagnosis of bipolar affective disorder.
5. Hepatic impairment:
  - Dose should be decreased in hepatic impairment:

6. Renal:

- Reduce dose if Cr Cl < 30 mL/minute and in haemodialysis patients.

7. Epilepsy:

- Epilepsy/ history of seizures
- Other risks for reduced seizure threshold, including treatment with drugs that may increase the risk of seizures

8. Bleeding: <sup>2</sup>

- SNRIs, (like the SSRIs) may increase the risk of bleeding, especially gastrointestinal bleeding, by blocking the uptake of serotonin into platelets.

However, the absolute risk of this is **low**

Use with caution if the patient is at high risk of bleeding (e.g. age >80 years or previous upper GI bleeding) or taking drugs known to increase risk of GI bleeding (regular aspirin or NSAIDs).

### Pregnancy

Venlafaxine is a category B2 drug with respect to pregnancy.

Category B2 drug 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 are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Most studies have suggested maternal use of venlafaxine is not been associated with an increased risk of congenital malformations.

Associations between maternal exposure to venlafaxine and increased risks of spontaneous abortion and preterm delivery have been reported, however the data are inconsistent and likely confounded by indication and other factors.

Neonatal withdrawal symptoms include respiratory distress, irritability, temperature instability, sleep disturbance, tremors, jitteriness, feeding difficulties and diarrhoea, which can be attributed to serotonergic hyperstimulation may develop due to prenatal exposure to venlafaxine, especially during the latter stages of pregnancy.

If venlafaxine is the medicine of choice, use the lowest effective dose and inform neonatal care providers about the maternal use of venlafaxine as supportive care may be required.

Long term behavioural and cognitive outcomes of in utero exposure to venlafaxine in humans are limited. A recent study found no differences in neurodevelopmental outcomes between the exposed and non-exposed children .

### Breastfeeding

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

If venlafaxine is the medicine of choice, use the lowest effective dose and closely observe the breastfed infant for adverse effects such as sleeping difficulties, poor feeding and restlessness (13). Inform neonatal care providers immediately if any adverse effects are noted in the breastfed infant.

There is still a lack of information regarding the neurodevelopmental outcomes of infants exposed to venlafaxine via breast milk.

### Adverse Effects

These include:

1. CVS:
  - Palpitations/ tachycardia
  - Orthostatic hypotension
  - Increased BP
  - SNRIs have also been associated with **stress-induced (takotsubo) cardiomyopathy.**
  - Prolonged QT interval
2. CNS effects:
  - Serotonergic effects which occur in children > adolescents > adults.

These may include:

- ♥ Anxiety / agitation
- ♥ Panic attacks
- ♥ Insomnia
- ♥ Tremor

- Seizures:
  - ♥ SNRIs may increase the risk of seizures (risk less than with TCAs).

The risk is dose-dependent and is greatest at the start of treatment and when there is a dose increase; use low doses and titrate slowly.

### 3. Serotonin toxicity:

- A more serious serotonin toxicity can develop, particularly when used in combination with other serotonergic agents.

Treatment with either moclobemide or a MAOI (or within 14 days of stopping a MAOI or within 2 days of stopping moclobemide) is contraindicated due to the risk of serotonin toxicity.<sup>2</sup>

### 4. Hyponatraemia:

- Usually occurs early in treatment, may be asymptomatic, and is part due to SIADH.
- Treatment with drugs that may cause hyponatraemia may also increase the risk of SNRI-induced hyponatraemia.

### 5. Sexual dysfunction:

- e.g. impotence, decreased libido

### 6. Increased suicidal thoughts:

- **Increased** suicidal thoughts and behaviour can occur **soon after** starting any antidepressants, particularly in young people; monitor patients frequently and carefully **early** in treatment.

## Dosing

### Adults:

- 75 mg once daily; if required, increase to 150 mg once daily.

Although most people will respond to doses of 150 mg daily or less, doses of up to 225 mg daily may be needed in some cases.

Little is known about efficacy and safety above 225 mg daily.

Renal impairment:

CrCl < 30 mL/minute, dialysis, adult, halve dose; titrate carefully against clinical effects.

Hepatic impairment:

Adult, initially halve dose, then titrate carefully against clinical effects.

Ceasing treatment:

When ceasing treatment the taper dose over at least 2 weeks, in order to minimise risk of withdrawal effects.

References

1. eTG - November 2019.
2. Venlafaxine in Australian Medicines Handbook Website, July 2019.
3. Venlafaxine in MIMs Website, 1 May 2019.
4. RWH Pregnancy & Breastfeeding Guidelines, 21 May 2019.

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