

DESVENLAFAXINE

Introduction

Desvenlafaxine (trade name in Australia, “Pristiq” among others) is a potent selective **serotonin *and* noradrenaline** reuptake inhibitor (**SNRI**).

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

Desvenlafaxine is an **active metabolite** of **venlafaxine** and so it is essentially the **same agent** as **venlafaxine**.

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.

Desvenlafaxine was introduced into clinical practice in the US and in Australia in 2008.

Chemistry

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

Desvenlafaxine is the **active metabolite** of **venlafaxine**.

Classification

Antidepressants can be loosely classified into 6 groups:

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

TCA's 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.

Preparations

Desvenlafaxine succinate as:

Controlled release tablets:

- 50 mg
- 100 mg

Mechanism of Action

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

Desvenlafaxine 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.

Pharmacodynamics

Desvenlafaxine 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 desvenlafaxine is far more **toxic in overdose** than is the case with the SSRIs.

Pharmacokinetics

Absorption:

- Desvenlafaxine is administered orally.

It is well absorbed, with an absolute oral bioavailability of 80%.

Distribution

- Desvenlafaxine's volume of distribution at steady state following intravenous administration is 3.4 L/kg
- Protein binding is modest at around 30%.
- Desvenlafaxine can cross the human placenta.
- Desvenlafaxine is distributed into human breast milk in small amounts only.

Metabolism and excretion:

- Around 55% of desvenlafaxine is metabolized, mostly via the CYP3A4 system in the liver.
- Approximately 45% of desvenlafaxine is excreted unchanged in urine.
- Elimination half-life is around 11 hours.

Indications

Desvenlafaxine is indicated for the treatment of **major depression**.

Contra-indications/precautions

These include:

1. Hypersensitivity to desvenlafaxine.
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: ²
 - 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: ²

- 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

Desvenlafaxine is classed as 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.

Published reports describing maternal use of desvenlafaxine have not been located.

Desvenlafaxine is the active metabolite of venlafaxine. Consultation with a perinatal psychiatrist is recommended if the initiation or continuation of desvenlafaxine therapy is required during pregnancy.

Most studies have shown that venlafaxine has not been associated with an increased risk of birth defects.

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.

Similar to venlafaxine, newborns exposed to desvenlafaxine, especially in late pregnancy, may experience self-limiting neonatal withdrawal symptoms.

These symptoms include respiratory distress, irritability, problems sleeping, tremor, jitteriness and feeding difficulties. Inform neonatal care providers about the maternal use of desvenlafaxine as supportive care may be required.

There is still a lack of information regarding the long term behavioural and cognitive outcomes of infants exposed to desvenlafaxine in utero.

Breast feeding

Small amounts of desvenlafaxine are excreted into breast milk, but these amounts are unlikely to cause harmful effects in the breastfed infant.

In women who choose to breastfeed their healthy full-term infant while taking desvenlafaxine, use the lowest effective daily dose and observe the breastfed infant for adverse effects such as irritability, poor feeding, restlessness and unusual sleeping pattern changes.

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 desvenlafaxine 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.²

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

Usual adult dosing is:

- Oral 50 mg once daily.

Most people will not benefit from doses > 50 mg daily.

However if higher dosing is considered necessary, increase the dose at intervals of **at least 7 days**.

Maximum dosing is 200 mg once daily.

Renal impairment:

CrCl < 30 mL/minute:

- Oral, initially 50 mg every second day.

References

1. eTG - November 2019.
2. Desvenlafaxine in Australian Medicines Handbook Website, Accessed November 2019.
3. Desvenlafaxine in MIMs Website, 1 June 2017.
4. Desvenlafaxine in RWH Pregnancy & Breastfeeding Guidelines, 18 August 2017.

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