

SNRIs

Venlafaxine is prescribed for individuals diagnosed with depression or generalised anxiety disorder. Duloxetine is an SNRI but is not commonly prescribed for psychiatric diagnoses in the UK.

How the SNRI's interact with/affect the brain
The theory behind how SNRI's and other antidepressants elevate individuals mood is based around the assumption that individuals who are feeling depressed have reduced levels of neurotransmitters, particularly serotonin and noradrenaline in the brain. Neurotransmitters are released from neurons (cells found in the brain and other parts of the nervous system) and act as messengers, passing signals between neurons. For example, when a nerve impulse arrives at a serotonergic neuron (also known as a pre-synaptic neuron), serotonin is released from the cell and diffuses through a space between two neurons, called the synaptic cleft. Serotonin then binds to specific serotonin receptors on a different neuron (post-synaptic neuron) producing a specific signal, impulse or effect. Serotonin is then released from its receptors and 're-absorbed' into the pre-synaptic neuron, or degraded by enzymes in the synaptic cleft.

It is a similar mechanism through which noradrenaline is released from a noradrenergic (noradrenaline releasing) pre-synaptic neuron, binds to noradrenaline receptors on the post-synaptic neuron and is then 're-absorbed' into the neuron it was originally released from.

When a SNRI is introduced into the body, it attaches itself to the 're-absorbing' receptors for serotonin and noradrenaline on the pre-synaptic neuron, therefore enabling serotonin and noradrenaline to stay in the synaptic cleft for longer and they will have a greater chance of re-attaching to a serotonin or noradrenaline receptors on the post synaptic neuron and generating further impulses/signals. Daily doses of Venlafaxine of 150 mg or less, do not exert any effect on noradrenaline re-uptake and so acts in a similar manner to an SSRI. Daily doses of Venlafaxine greater than 150 mg inhibits re-uptake of both serotonin and noradrenaline. Potential abnormal synapse activity upon withdrawal of SNRI Long term increased synaptic serotonin and noradrenaline, causes a down regulation of post synaptic serotonin and noradrenaline receptors. There is also an increase in serotonin and noradrenaline re-uptake transporters, due to long term blockage, resulting in an increased re-uptake of serotonin and noradrenaline from the synaptic cleft into the pre-synaptic neuron. This leads to an overall decrease in serotonin and noradrenaline transmission which may produce withdrawal effects. **BNF Doses**

The dose listed below is the maximum safe amount an individual theoretically could be prescribed daily. However, the usual 'therapeutic' doses will vary depending on the individual and the prescriber. Venlafaxine: Adult max = 375 mg
Drug specific side-effects
Commoner side effects include; Constipation, nausea, dizziness, dry mouth, insomnia, nervousness, drowsiness, asthenia (weakness or loss of strength), headache, sexual dysfunction, sweating, anorexia (loss of appetite), weight changes, diarrhoea, dyspepsia (indigestion), vomiting, abdominal pain, high blood pressure, palpitations (sensations of heart beating fast), changes in blood cholesterol, chills, pyrexia (fever), shortness of breath, yawning, abnormal dreams, agitation, anxiety, confusion, hypertonia (increased muscle tone), paraesthesia (spontaneous tingling sensations), tremor, urinary frequency, menstrual disturbances, arthralgia (painful joints), myalgia (pain in the muscles), visual disturbances, ringing in the ears, rashes. Less commonly; taste disturbances, postural hypotension (low blood pressure upon standing, can lead individuals to faint), arrhythmias, hyponatraemia (low sodium in the blood), hallucinations, myoclonus (sudden spasm of muscles), urinary retention, bleeding disorders, hypersensitivity reactions
Rarely; ataxia (shaky movements and unsteady gait), inco-ordination, speech disorder, mania and hypomania, seizures, galactorrhoea (milk production and secretion from the breasts), thrombocytopenia (reduced levels of platelets), hepatitis (inflammation of the liver). There may be other side-effects of taking Venlafaxine which are not listed above, those listed are just the more commonly seen side-effects or the acknowledged ones.

Withdrawal/Discontinuation
When discussing coming off psychiatric drugs the terms withdrawal and discontinuation will be used interchangeably. Although the term withdrawal is usually associated with coming off drugs to which an individual is addicted to, when an individual comes off SNRI's they are not addicted to the drug, they do not consciously crave the drug. The effects an individual may experience when withdrawing/discontinuing/reducing a SNRI are not related to addiction but rather to the body struggling to adapt to the absence of a chemical it has become used to being present. Withdrawal effects Reported adverse effects upon venlafaxine withdrawal include; (the most commonly reported effects are highlighted in italics) • Diffuse headache

- Nausea
- Feelings of abdominal distension
- Fatigue
- Tinnitus (ringing in the ears)
- Congested sinuses
- Insomnia
- Dysphoria (state of dissatisfaction or unease)
- Dizziness or lightheadedness
- Excessive sweating
- Irritability
- Vertigo (feels like you or the environment are rotating constantly)
- Depression
- Paraesthesia (spontaneous abnormal tingling sensations)
- Auditory Hallucinations
- Chills
- Urinary frequency (passing urine more frequently)

- 'Bizarre' dreams
- Shock like sensation in the head and neck when turning head suddenly
- Diarrhoea
- Ataxia (shaky movements and unsteady gait)
- Cramps
- Arthralgia (painful joints)

If a symptom is due to withdrawal of a drug, it will typically occur soon after a reduction (or discontinuation) of the drug and disappear within about 2 weeks (and generally not persist beyond 3 weeks). Symptoms usually occur with 36-48 hours following discontinuation (or reduction); however delayed withdrawal reactions have been reported to occur upon 1 week after discontinuation. Although there is not a recognised Venlafaxine withdrawal syndrome, many of the withdrawal effects experienced mirror those seen in SSRI discontinuation. This has led authors to speculate that a similar mechanism may be responsible for SSRI and SNRI withdrawal symptoms. Venlafaxine at low doses works in a similar way to SSRI's, only at higher doses does Venlafaxine have a dramatic effect on inhibition of noradrenaline re-uptake. Therefore a similar approach could be taken when attempting Venlafaxine withdrawal as one could when attempting SSRI withdrawal. The three primary risk factors for developing withdrawal symptoms when discontinuing a SSRI are;

- long duration of anti-depressant treatment
 - abrupt withdrawal from the SSRI
 - withdrawing from SSRI's with short half-lives
- Withdrawal effects have been reported to occur with both abrupt and more gradual withdrawal but seem to be reduced by a truly gradual withdrawal that lasts at least two to three months.

Rates of withdrawal We would recommend that at least two weeks should pass between each dose reduction. As for how much to reduce the dose by, this is not a finite science. Some individuals are able to come off all at once without any problems, whereas others develop severe withdrawal effects. Reducing in 10% steps would seem to be a sensible target, especially if the drug has been taken consistently for over a year. A maximum of 25% reduction every 2 weeks is probably the fastest you could sensibly attempt to reduce, however, it should be borne in mind that the more gradual the reductions the more time the brain has to adapt and fewer withdrawal effects experienced. But ultimately the choice as to how fast and how much to reduce by is the individuals. Example 1

So if an individual was taking 150mg Venlafaxine a day and wanted to reduce the drug by 10% every two weeks, the first 2 weeks they would take 135mg a day, the next 2 weeks 120mg a day etc. Approximately 5 months later they would have fully come off the drug. However, if after 4 weeks they found that they were developing withdrawal effects it would perhaps be sensible to avoid further reductions until they no longer felt the withdrawal effects and if they felt the need to increase the dose by 10% until the withdrawal effects subsided they did this. Also, they could decide to reduce in smaller steps from that point on rather than the original 15mg steps to further avoid developing unpleasant withdrawal effects. Venlafaxine is available in 37.5mg tablets (minimum tablet dose) which could make things tricky, trying to cut the tablets to reduce in 15mg amounts. Alternative way to withdraw from Venlafaxine

Venlafaxine has a half-life of 5 hours which is relatively short and studies looking at selective serotonin re-uptake inhibitor (SSRI) withdrawal demonstrate that individuals who withdraw from an SSRI with a longer half-life are less likely to experience any withdrawal effects.

It is possible to switch to an SSRI with a long half-life (Fluoxetine) and withdraw from that. The equivalent dose of 75mg Venlafaxine is 20mg Fluoxetine. Fluoxetine is also available in liquid form which makes it easier to reduce the dose by 10%, so you could speak to your doctor about prescribing Fluoxetine liquid. It is advised that you then 'stabilise' on the liquid Fluoxetine for 2-4 weeks before beginning the dose reductions/withdrawal. Example 2

So if an individual was taking 150mg Venlafaxine a day, they would convert to 40mg Fluoxetine per day (preferably liquid). To reduce the drug by 10% every two weeks, the first 2 weeks they would take 36mg per day, the next 2 weeks 32mg per day etc. Approximately 5 months later they would have fully come off the drug.

As with the previous example, if the individual was developing withdrawal effects they could avoid further reductions until they no longer felt the withdrawal effects and if they felt the need to increase the dose by 10% until the withdrawal effects subsided they did this. Also, they could decide to reduce in smaller steps from that point on (e.g. reduce by 2 mg every 2 weeks). Even if you are not successful in coming off your medication at the first attempt you will probably learn from the experience, what was beneficial, what could you have done differently and ultimately had an opportunity to evaluate the role of the drug in your life.

Interactions If you are taking any medications other than your psychiatric drugs it is worthwhile speaking to your GP about what potential interactions your psychiatric medications may have with your other medications. Listed below are interactions that occur between some psychiatric drugs. If you are taking Venlafaxine and other types of psychiatric drugs it is worthwhile reading through the interactions section to work out which drug you should reduce first.

Venlafaxine increases plasma concentrations of Clozapine and Haloperidol therefore come off of Clozapine or Haloperidol before reducing Venlafaxine