Review on Venlafaxine Hydrochloride mechanism of Action, Therapeutic indications and Overview on analytical method for Venlafaxine

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ABSTRACT:
Depression is one of the largest reasons of non-fatal health loss worldwide. Second-generation antidepressant drugs are the first-line therapy for pharmacological management of depression. Improvement in the use of these drugs is significant in lowering the burden of depression. Venlafaxine is a unique antidepressant drug including a wide range of antidepressant activity and a safety profile that are corresponding to serotonin selective reuptake inhibitors. Venlafaxine (VEN) is an antidepressant agent which is widely used as an alternative to selective serotonin reuptake inhibitors (SSRIs), particularly for the treatment of SSRI-resistant depression. Venlafaxine inhibits presynaptic reuptake of serotonin (5-hydroxytryptamine; 5-HT) and noradrenaline (norepinephrine). As the co-administration of antidepressant drugs with other medications is very common in clinical practice, the potential risk for pharmacokinetic and/or pharmacodynamic drug interactions that may be clinically meaningful increases. Bearing in mind that VEN has exhibited large variability in antidepressant response, besides the individual genetic background, several other factors may contribute to those variable clinical outcomes, such as the occurrence of significant drug-drug interactions. Indeed, the presence of drug interactions is possibly one of the major reasons for interindividual variability, and their anticipation should be considered in conjugation with other specific patients’ characteristics to optimize the antidepressant therapy. Hence, a comprehensive overview of the pharmacokinetic- and pharmacodynamic-based drug interactions involving VEN is herein provided, particularly addressing their clinical relevance.

Keywords: Venlafaxine, Serotonin reuptake inhibitor, Depression, Drug-drug interaction, Clinical relevance, Noradrenaline.

INTRODUCTION:
Venlafaxine is a unique antidepressant with a broad spectrum of antidepressant activity and a safety profile that resembles serotonin selective reuptake inhibitors. Venlafaxine is FDA approved to treat and manage symptoms of depression, social anxiety disorder, and cataplexy. Venlafaxine inhibits presynaptic reuptake of serotonin (5-hydroxytryptamine; 5-HT) and noradrenaline (norepinephrine). [1] Venlafaxine extended-release (XR) has been investigated in patients with major depression and in patients with major depression with associated anxiety in randomised, double-blind, multicentre trials. Off-label venlafaxine can be used for brain damage, hot flashes, diabetic neuropathy, fibromyalitis, and complex pain syndromes, prevention of migraine, post-traumatic stress disorder, obsessive-compulsive syndrome, and premenstrual disorders. Venlafaxine may be used independently or as part of combination therapy with other drugs. This review outlines the therapeutic indications of venlafaxine, mechanism of action,
administration methods, its adverse effects, contraindications, toxicity, and monitoring, of venlafaxine so providers can direct patient therapy where it is indicated as part of the interprofessional team.[2,3]

### Drug Profile:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Venlafaxine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>[Chemical Structure Image]</td>
</tr>
<tr>
<td>IUPAC name</td>
<td>1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl] cyclohexan-1-ol</td>
</tr>
<tr>
<td>Molecular formula</td>
<td>C_{17}H_{27}NO_{2}</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>277.408 g/mol</td>
</tr>
<tr>
<td>Class</td>
<td>Antidepressant-Agents(Serotonin-norepinephrine reuptake inhibitor)</td>
</tr>
<tr>
<td>Solubility</td>
<td>Water</td>
</tr>
<tr>
<td>Melting point</td>
<td>215-217 °C</td>
</tr>
<tr>
<td>Dosage form</td>
<td>Tablet, Capsule</td>
</tr>
<tr>
<td>BCS Classification</td>
<td>Class-I (High solubility &amp; High permeability)</td>
</tr>
</tbody>
</table>

Table- Drug Profile of Venlafaxine
MECHANISM OF ACTION:

Venlafaxine belongs to a class of antidepressant drugs called serotonin norepinephrine reuptake inhibitors (SNRIs). SNRIs work by increasing the levels of substances called serotonin and norepinephrine in your brain.

Figure: Mechanism of Action of Venlafaxine

Venlafaxine works by increasing serotonin levels, norepinephrine, and dopamine in the brain by blocking transport proteins and stopping its reuptake at the presynaptic terminal. This action leads to more transmitter at the synapse and ultimately increases the stimulation of postsynaptic receptors. SNRIs act primarily upon serotonergic and noradrenergic neurons but have little or no effect upon cholinergic or histaminergic receptors. Venlafaxine is a bicyclic phenylethylamine compound. Venlafaxine is a more potent inhibitor of serotonin reuptake than norepinephrine reuptake. Venlafaxine is essentially a selective serotonin reuptake inhibitor at 75 mg, and with higher doses such as 225 mg/day, it has significant effects on the norepinephrine transporter in addition to serotonin.[4,5]

PHARMACOLOGY:

Pharmacodynamics:

The mechanism of venlafaxine's antidepressant effect is believed to be due to their potentiation of neurotransmitter activity in the central nervous system through the inhibition of the reuptake of serotonin and norepinephrine from within the synapse. Venlafaxine has also been shown to weakly inhibit dopamine reuptake.[6,7] Neither venlafaxine nor ODV bind to muscarinic, histaminergic, or alpha-1 adrenergic receptors; pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Hyponatremia has also been shown to occur as a result of treatment with SNRIs, and is associated with the development of the syndrome of inappropriate antidiuretic hormone secretion (SIADH).[8]
Venlafaxine also demonstrates a clinically significant and dose-related effect on blood pressure, likely due to its potentiation of norepinephrine.[9]

**Pharmacokinetics:**

VEN consists of a racemic mixture of R(+) and S(-) enantiomer. The (R) enantiomer has been shown to exhibit greater serotonin reuptake inhibition property, while the (S) enantiomer inhibits the reuptake of both monoamines.[10] VEN is highly metabolized in humans with a urinary excretion of the unchanged compound between 1-10 % of an administered dose. Demethylation to O-desmethylvenlafaxine (ODV) is the primary route of the first pass metabolism of VEN. Cytochrome P450 2D6 (CYP2D6) is the major enzyme involved in ODV formation. ODV gets excreted unchanged and as its glucuronide.[11] A few studies describe a possible stereoselective metabolism of VEN to ODV with either selection towards the (S) isomer or the (R) isomer but the majority of studies regarding VEN pharmacokinetics and antidepressant response in association with CYP2D6 metabolizer phenotype do not distinguish between the enantiomers.[12]

**USES:**

Venlafaxine is used to treat depression. It may improve your mood and energy level, and may help restore your interest in daily living. Venlafaxine is known as a serotonin-norepinephrine reuptake inhibitor (SNRI). It works by restoring the stability of some natural substances like serotonin and norepinephrine activity in the brain.[13]

**SIDE EFFECTS:**

Cardiovascular side effects from antidepressant drugs, including clinically significant blood pressure changes, conduction disturbances, and arrhythmias may complicate long-term therapy. Cardiovascular effects are most common with tricyclic antidepressants, but occur rarely with most antidepressants. Venlafaxine is a unique antidepressant with a broad spectrum of antidepressant activity and a safety profile that resembles serotonin selective reuptake inhibitors. Discontinuation rates because of unsatisfactory clinical response were similar among patients treated with Venlafaxine XR, Fluoxetine or Paroxetine. Adverse events affecting to the digestive system (nausea, dry mouth), nervous system i.e. dizziness, insomnia) and abnormal ejaculation systems as well as sweating are the most commonly occurring side effects during treatment. Different studies related to Paroxetine and Fluoxetine shows nearly similar side effects to Venlafaxine drug.[14,15]

Common side effects of Venlafaxine are as follows:

- headaches
- dry mouth
- sweating
- trouble sleeping
- feeling dizzy
- feeling sleepy
- constipation
- feeling sick

**ANALYTICAL METHODS FOR VENLAFAXINE:**

- UV Spectroscopic method
  
  UV-Visible spectroscopic method is one of the most accepted analytical techniques. The reason is that this technique is multipurpose and can detect almost all molecules. With UV-Vis spectroscopy, the UV-Vis light is passed through a sample and the transmittance of light by a sample is measured. From the transmittance (T), the absorbance can be calculated as \( A = \log(T) \). An absorbance spectrum is obtained
that shows the absorbance of a compound at different wavelengths. The amount of absorbance at any wavelength is due to the chemical structure of the molecule.[16,17]

UV-Visible technique can be used for qualitative analysis, to identify functional groups in molecules and identification of a compound by matching the absorbance spectrum. It can also be used in a quantitative manner, as concentration of the analyte is related to the absorbance using Beer’s Law.[18,19] UV-Vis spectroscopy is used to quantify the amount of DNA or protein in a sample, for water analysis, and as a detector for many types of chromatography. Kinetics of chemical reactions are also measured with UV-Vis spectroscopy by taking repeated UV-Vis measurements over time. UV-Vis measurements are generally taken with a spectrophotometer. UV-VIS spectroscopy is also a very popular detector for some other analytical techniques, like chromatographic techniques, because it can detect almost all compounds.[20]

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Drug</th>
<th>Method</th>
<th>Description</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Venlafaxine HCl in bulk and pharmaceutical dosage form</td>
<td>UV Spectrophotometry</td>
<td>Wavelength-274 nm Solvent-0.1 N HCL</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>Venlafaxine HCl in bulk and pharmaceutical dosage form</td>
<td>UV-VIS</td>
<td>Wavelength-227 nm Solvent-Water: Methanol (50:50)</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>Venlafaxine in bulk and formulations</td>
<td>UV Spectrophotometry</td>
<td>Wavelength-222 nm Solvent- Phosphate buffer</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>Venlafaxine in bulk and pharmaceutical formulations</td>
<td>UV-VIS</td>
<td>Wavelength-223 nm Solvent- 0.1 N NaOH</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>Venlafaxine in pure and pharmaceutical formulations</td>
<td>UV Spectrophotometry</td>
<td>Wavelength-226 nm Solvent- Acetonitrile: Water (20:80)</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>Venlafaxine in solid dosage form</td>
<td>UV Spectrophotometry</td>
<td>Wavelength-225.27 nm Solvent-Distilled water</td>
<td>26</td>
</tr>
<tr>
<td>7</td>
<td>Venlafaxine in pure and pharmaceutical formulation</td>
<td>UV Spectrophotometry</td>
<td>Wavelength-225 nm Solvent-Water</td>
<td>27</td>
</tr>
<tr>
<td>8</td>
<td>Venlafaxine in bulk and pharmaceutical dosage form</td>
<td>UV-VIS spectroscopy</td>
<td>Wavelength-225.20 nm Solvent-Distilled water</td>
<td>28</td>
</tr>
</tbody>
</table>

- FTIR Spectroscopy:
  Venlafaxine HCL discs were prepared by pressing the VF-HCl with potassium bromide and the spectra between 4000 to 500 cm was obtained under the operational conditions. The absorption maximum in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum.
CONCLUSION:
Venlafaxine XR has shown efficacy in the treatment of major depression and was at least as effective as Fluoxetine or Paroxetine and more effective than Venlafaxine IR. Furthermore, it is effective at reducing symptoms of anxiety in depressed patients. The occurrence of the side effects in Venlafaxine XR is likely similar to that of patients that gets treatment with well established selective serotonin reuptake inhibitors. As an effective and well tolerated antidepressant, Venlafaxine XR should be considered as a first-line pharmacological treatment in patients with major depression.

In another conclusion, venlafaxine is a safe and well-tolerated analgesic drug for the symptomatic treatment of neuropathic pain, and there is limited evidence that high-dose venlafaxine (150 mg/day) can be even more beneficial. While the present evidence is quite encouraging regarding venlafaxine’s use for neuropathic pain, further research is needed to continue to expand on these findings, particularly when in consideration with other possible pharmacological agents.

REFERENCES:


