IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

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

Mr.Mahesh B. Kshirsagar, Mr. Sanjay S. Popale
SAJVPM's College of Pharmaceutical science & Research Centre ,Kada

ABSTRACT:

Depression is the one of the largest reason 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, fibromyositis, 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:

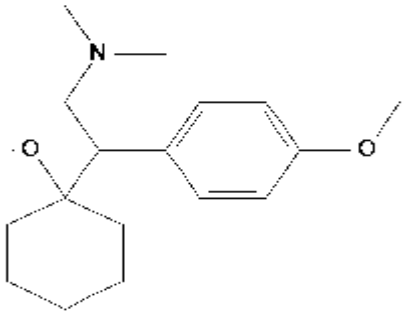
Drug	Venlafaxine
Structure	
IUPAC name	1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexan-1-ol
Molecular formula	$C_{17}H_{27}NO_2$
Molecular weight	277.408 g/mol
Class	Antidepressant-Agents(Serotonin-norepinephrine reuptake inhibitor)
Solubility	Water
Melting point	215-217 °C
Dosage form	Tablet, Capsule
BCS Classification	Class-I (High solubility & High permeability)
Dose	

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.

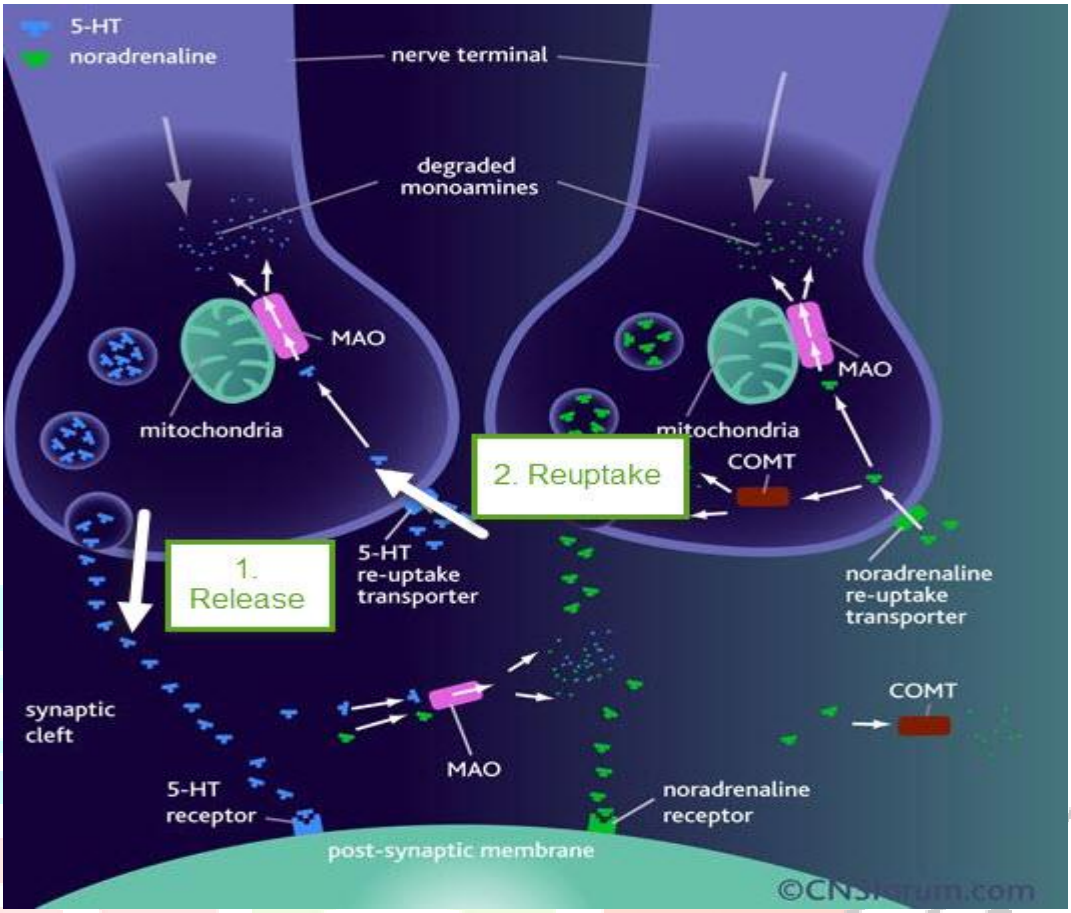


Figure: Mechanism of Action of Venlafaxine

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) isoform or the (R) isoform 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 substanceslike 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]

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

- 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 safeand well-tolerated analgesic drug for the symptomatictreatment of neuropathic pain, and there is limitedevidence that high-dose venlafaxine (150 mg/day)
can be even more beneficial. While the present evidence is quite encouraging regarding venlafaxine'suse for neuropathic pain, further research isneeded to continue to expand on these findings,particularly when in consideration with other possiblepharmacological agents.

In 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:

1. Yanbo Zhang, Xiaoying Bi et al. Venlafaxine Improves the Cognitive Impairment and Depression-Like Behaviors in a Cuprizone Mouse Model by Alleviating Demyelination and Neuroinflammation in the Brain, Front. Pharmacol. 10:332.
2. Saad MA, El-Sahar AE, Sayed RH, Elbaz EM, Helmy HS, Senousy MA. Venlafaxine Mitigates Depressive-Like Behavior in Ovariectomized Rats by Activating the EPO/EPOR/JAK2 Signaling Pathway and Increasing the Serum Estradiol Level. Neurotherapeutics. 2019 Apr;16(2):404-415.
3. Fava GA, Benasi G, Lucente M, Offidani E, Cosci F, Guidi J. Withdrawal Symptoms after Serotonin-Noradrenaline Reuptake Inhibitor Discontinuation: Systematic Review. Psychother Psychosom. 2018;87(4):195-203.
4. Ning J, Luo J, Meng Z, Luo C, Wan G, Liu J, Wang S, Lian X, Melgiri ND, Sun Y, Huang R. The efficacy and safety of first-line therapies for preventing chronic post-surgical pain: a network meta-analysis. Oncotarget. 2018 Aug 10;9(62):32081-32095.
5. Thase ME, Clayton AH, Haight BR, Thompson AH, Modell JG, Johnston JA: A double-blind comparison between bupropion XL and venlafaxine XR: sexual functioning, antidepressant efficacy, and tolerability. J Clin Psychopharmacol. 2006 Oct;26(5):482-8.
6. Strawn JR, Geracioti L, Rajdev N, Clemenza K, Levine A. Pharmacotherapy for generalized anxiety disorder in adult and pediatric patients: an evidence-based treatment review. Expert Opin Pharmacother. 2018 Jul;19(10):1057-1070.
7. Gallagher HC, Gallagher RM, Butler M, Buggy DJ, Henman MC. Venlafaxine for neuropathic pain in adults. Cochrane Database Syst Rev. 2015; 23(8):CD011091.
8. Caspi A, Sugden K, Moffitt TE, et al., 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science.2018; 301(5631):386–389.
9. Smith D, Dempster C, Glanville J, et al.Efficacy and tolerability of venlafaxine compared with selective serotonin reuptake inhibitors and other antidepressants: a meta-analysis. Br J Psychiatry 2002; 180:396–404.
10. Holliday SM, Benfield P. Venlafaxine. A review of its pharmacology and therapeutic potential in depression. Drugs. 1995; 49(2):280-294.
11. Justyna Suwała, Marta Oleś, Anna Wiela-Hojeńska, Adverse effects of venlafaxine therapy and risk factors for their occurrence, Pharmacotherapy in Psychiatry and Neurology. 2019; 34(4):285-304.

12. Melad G. Paulis, Essam M. Hafez, Nashwa F. El-Tahawy, Mohmed K. M. Aly, Toxicological Assessment of Venlafaxine: Acute and Subchronic Toxicity Study in Rats, International Journal of Toxicology. 2018; 37(4):327-334.
13. Roxanas M, Hibbert E, Field M: Venlafaxine hyponatraemia: incidence, mechanism and management. Aust N Z J Psychiatry. 2007 May;41(5):411-8.
14. MontgomerySA.Tolerability of serotonin norepinephrine reuptake inhibitor antidepressants. CNS Spectrums 2008;13(11):27–33.
15. Barbui C, Hotopf M, Freemantle N, Boynton J, Churchill R, Eccles MP, et al. Selective serotonin reuptake inhibitors versus tricyclic and heterocyclic antidepressants: comparison of drug adherence. Cochrane Database of Systematic Reviews. 2000;(1).
16. Skoog, Douglas A.; Holler, F. James; Crouch, Stanley R. (2007). Principles of Instrumental Analysis (6th ed.). Belmont, CA: Thomson Brooks/Cole. pp. 169–173.
17. Sooväli, L.; Rõõm, E.-I.; Kütt, A.; et al. (2006). "Uncertainty sources in UV–Vis spectrophotometric measurement". Accreditation and Quality Assurance. 11 (5): 246–255.
18. Namioka T. Diffraction Gratings. In: Vacuum Ultraviolet Spectroscopy. Vol 1. Experimental Methods in Physical Sciences. Elsevier; 2000:347-377.
19. Bosch Ojeda C, Sanchez Rojas F. Recent applications in derivative ultraviolet/visible absorption spectrophotometry: 2009–2011. Microchem J. 2013;106:1-16.
20. Domingo C, Saurina J. An overview of the analytical characterization of nanostructured drug delivery systems: Towards green and sustainable pharmaceuticals: A review. Anal Chim Acta. 2012;744:8-22.
21. Lavanya K et al. New Simple UV Spectrophotometric Method For Determination of Venlafaxine Hydrochloride in Bulk And Pharmaceutical Dosage Forms, International Journal of Pharmaceutical Quality Assurance.2013; 4(1):1-3.
22. Dhiraj Kumar et al. Method development and estimation of Venlafaxine Hydrochloride in bulk and Pharmaceutical dosage forms using UV-VIS Spectrophotometer, Int. J. Drug Dev. & Res., October - December 2013; 5(4):133-139.
23. C. Sowmya et al. Development and Validation of Spectrophotometric Method for the estimation of Venlafaxine in Bulk and Formulations, Int. J. Chem. Sci. 2011; 9(1): 52-58.
24. Bhagyashree A. Pakhale et al. Development and Validation of Spectrophotometric Method for Determination of Venlafaxine Hydrochloride, International Journal of Pharma Sciences and Research. 2015; 6(1):66-69.
25. Radha Sharma et al. UV-Spectrophotometric Estimation of Venlafaxine Hydrochloride, Asian Journal of Chemistry. 2009; 21(9):7440-42.
26. Nikhil A. Karani et al. Analytical method development & validation of venlafaxine hydrochloride in solid dosage forms using uv spectrophotometer, Journal of Pharmacy Research 2009; 2(7):1246-1249.
27. M. M. Eswarudu et al. New Simple UV Spectrophotometric method for Determination of Venlafaxine Hydrochloride in pure and Pharmaceutical Formulation, World Journal Of Pharmacy And Pharmaceutical Sciences. 2017; 6(7):1292-1300.
28. Bansode A.S. et al. Analytical Method Development and Estimation of Venlafaxine Hydrochloride in Bulk and Pharmaceutical Dosage Form by UV- Visible Spectrophotometer, International Journal of Innovative Science, Engineering & Technology. 2019; 6(10):131-138.