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REVIEW ARTICLE

A Systematic Review of Desvenlafaxine's Efficacy, Safety, Moa, and Adverse Effects in the Treatment of Major Depressive Disorders

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ABSTRACT

Desvenlafaxine (DVS) was a novel serotonin (5-HT) that was currently in clinical development for the treatment of major depressive disorder and vasomotor symptoms associated with menopause. Desvenlafaxine was originally synthesized as part of research project to discover structural analogs of 4-(2-(Dimethylamino)-1-(hydroxycyclohexy) ethyl phenol is the major active metabolite of the antidepressant, a medication used to treat major depressive, generalized anxiety and panic disorders. Literature survey revealed that few LC-MS methods have been reported for estimation of DVS in biological matrices.
Keywords: Desvenlafaxine, serotonin (5-HT), antidepressant

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CONTENTS

1. Introduction

Desvenlafaxine is an antidepressant that is an FDA-approved drug to treat major depressive disorder in adults. For healthy women who have contraindications to estrogen, desvenlafaxine can be used off-label to treat hot flashes during menopause. Although not FDA approved in adolescents, the TORDIA studies have shown that serotonin and norepinephrine reuptake inhibitors like venlafaxine have efficacy in treating major depressive disorder in treatment-resistant depression in adolescents. This activity will highlight the mechanism of action, adverse event profile, off-label uses, dosing, pharmacodynamics, pharmacokinetics, monitoring, relevant interactions of desvenlafaxine, pertinent for interprofessional team members during desvenlafaxine therapy.

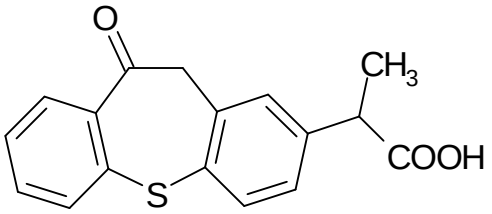


Fig 1: Chemical Structure

Objectives:

- Summarize the mechanism of action of desvenlafaxine.
- Identify the indications for using desvenlafaxine therapy.
- Outline the potential adverse events when using desvenlafaxine.
- Review the importance of interprofessional communication improving care coordination among the interprofessional team when initiating desvenlafaxine therapy.

Indicatios:

Desvenlafaxine is an antidepressant that is an FDA-approved drug to treat major depressive disorder in adults.[1] For healthy women who have contraindications to estrogen, clinicians can use desvenlafaxine off-label to treat hot flashes during menopause.[2] Although not FDA approved in adolescents, the TORDIA studies have shown that serotonin and norepinephrine reuptake inhibitors like venlafaxine have efficacy in treating major depressive disorder in treatment-resistant depression in adolescents.

2. Mechanism of action

Desvenlafaxine is an antidepressant medication that belongs to a category of drugs that inhibits the reuptake of both serotonin and norepinephrine, known as SNRIs. Desvenlafaxine is the primary active metabolite of venlafaxine. Therefore, the two agents are structurally similar in that they both contain two chemical rings that are not next to each other.[3] In vitro studies have shown that desvenlafaxine is ten times more selective for serotonin than for norepinephrine, making it similar to the drug duloxetine.[3] Surprisingly, the drug that desvenlafaxine derives from, venlafaxine, has an affinity to serotonin 30-times more than it does to norepinephrine. Currently, the time to inhibit reuptake in serotonin and norepinephrine is known for duloxetine, milnacipran, and venlafaxine. However, no such data is available for desvenlafaxine. Like the other SNRIs, there is a weak effect on dopamine and its reuptake [3].

Metabolism

The half-life of desvenlafaxine is 11 hours, and it metabolizes through the liver with a small amount broken down via the cytochrome P450 system. Since CYP enzymes are not significantly involved in its metabolism, there is not as large of a concern for drug-drug interaction as compared to its counterparts. Renal excretion is a major route of desvenlafaxine elimination. Nearly 45% of the medication is unchanged when eliminated in the urine. It is important to consider treating with a lower dose when dealing with patients who have moderate to severe renal impairment or end-stage renal disease.[3]

Administration:

Desvenlafaxine administration is via the oral route, and patients can take the drug with or without food. The dosage should be changed based on the patient's symptoms and their ability to tolerate the drug. The starting therapeutic dose is 50 mg. It comes in a 25-mg, 50-mg, and 100-mg tablet available only as an extended-release formulation. The 25-mg dose is a common choice for tapering off of the medication. The maximum dose of desvenlafaxine is 400 mg.

3. Adverse effects

Here is a broad range of general adverse effects that patients can experience with the usage of desvenlafaxine. A study comparing desvenlafaxine to a placebo in treating major depressive disorder in adolescents noted the most common side effects to be abdominal pain, decreased appetite, headache, and nausea. Less commonly noted were diarrhea, dizziness, and cough. As with most selective serotonin reuptake inhibitors (SSRIs), it is necessary to monitor for increased suicidal ideation. Abruptly stopping the use of desvenlafaxine can cause irritability, nausea, and headaches. Gradually tapering the medication is recommended to avoid such side effects.[4]

4. Contraindications

Prescribing this medication is contraindicated if a patient has a hypersensitivity to the drug or any components in its formulation. Although rare, serotonin syndrome is a very serious condition that carries a high mortality rate. Taking a thorough history and doing a proper medication reconciliation can help prevent this dangerous condition. Signs of serotonin syndrome include tachycardia, sialorrhea, hyperactive bowel sounds, mydriasis, hyperthermia, and diaphoresis. If unsure whether a patient is suffering from serotonin syndrome, the Sternbach and Hunter criteria can be useful to help arrive at a definitive diagnosis. It can be caused by combining monoamine oxidase inhibitors, tricyclic antidepressants, triptans, additional serotonin receptor modulators, and over-the-counter drugs such as St. Johns Wart. Desvenlafaxine therapy should not start until after discontinuing the previous class of medications listed for at least two weeks. If serotonin syndrome is suspected, prompt discontinuation of the offending agent is necessary, along with supportive measures. If necessary, cyproheptadine can be a therapeutic measure.[5]

There is conflicting data on gastrointestinal bleeding resulting from SNRI use. There is no specific documentation for this with desvenlafaxine; however, its

combined use with non-steroidal anti-inflammatory drugs may add to the risk.[6]

If a bipolar disorder is a consideration in the differential diagnosis, it is crucial to add a mood stabilizer along with a serotonin receptor modulator not to trigger a manic episode. There have been documented instances where neonates exposed to SNRIs late in the third trimester have gone on to develop difficulties with feeding and breathing, which have required prolonged hospitalization. Desvenlafaxine is a category C drug, which means that tests done on animals have shown an adverse effect on the fetus, and there are no well-controlled studies in humans. Still, possible benefits may justify the use of the drug in pregnant women despite the risks. Desvenlafaxine is excreted into breast milk, with one study reporting that peak levels are 3.3 hours after a dose. When mothers took the sister drug venlafaxine, neonates exposed to the drug via breast milk sometimes experienced poor neonatal adaptation. This reaction could occur in individuals taking desvenlafaxine as well.[7]

Monitoring: A detailed assessment of depression and suicidality should take place, especially at the beginning of therapy or when the dosage is changed. It is necessary to observe patients taking desvenlafaxine for behavior changes such as anxiety, social function, and mania.

Toxicity: Desvenlafaxine is rarely lethal when used as a standalone agent. There is a risk of serotonin syndrome when combined with other serotonin augmenting medications, triptans, tricyclic antidepressants, over-the-counter agents, and monoamine oxidase inhibitors. The treatment for overdose is symptomatic and supportive. There is no specific treatment for desvenlafaxine toxicity.

Enhancing Healthcare Team Outcomes

The interprofessional healthcare team, including clinicians, mid-level practitioners, nurses, mental health specialists, and pharmacists, should keep major depressive disorder in their differential when dealing with patients who may present with depressed mood, anhedonia, feelings of guilt, worthlessness, insomnia, and suicidality. Endocrine abnormalities, along with substance abuse, may also cause these symptoms. After ruling out substance misuse and other factors, only then should a psychiatric diagnosis of MDD should be made. It is now common to treat this disease with selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. Providers need to assess all the medications being taken by the patient to prevent drug interactions with desvenlafaxine, especially those with decreased glomerular filtration rate (GFR) or hepatic impairment. With inter professional care coordination and open information sharing, treating MDD with an SNRI like desvenlafaxine (or other agents in the antidepressant class) can be accomplished with greater therapeutic effectiveness and fewer adverse events and drug interactions.

Table 1: Analytical Method Details

Name of the Drug	Desvenlafaxine
Name of the Analyte	Desvenlafaxine
Molecular Formula of Desvenlafaxine	C16H25NO2
Molecular Weight of Desvenlafaxine	263.38 g/mol
Formula Weight of Desvenlafaxine	263.38 g/mol
Name of Internal Standard	Desvenlafaxine D6
Molecular Formula of Desvenlafaxine D6	C16H19 D6NO2
Molecular Weight of Desvenlafaxine D6	269.41 g/mol
Formula Weight of Desvenlafaxine D6	269.41 g/mol
Calibration	1.002 ng/mL to 1000.165 ng/mLng/Ml
Range for Desvenlafaxine	1.002 ng/mL
LLOQ for Desvenlafaxine	Liquid-Liquid Extraction
Sample Processing Method	LC-MS/MS
Instrument Method	K2EDTA

Table 2: Molecular Structures

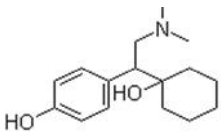
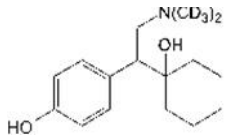
Desvenlafaxine	**Desvenlafaxine D6**
 Formula weight- 263.38g/mol	 Formula weight- 269.41g/mol

Table 3: Instrumental conditions

Standard	Supplier	Assay Purity (%)	Batch/ Lot No.	Retest / Expiry Date
Desvenlafaxine	Clearsynth	99.98%	CS-DE-238	07 Jan 2014
Desvenlafaxine - D6	Splendid Labs	99.52%	SLD-DV-058	14 Mar 2014

Table 4: Chemicals

S.No	Chemicals	Grade
01	Methanol	Gradient/HPLC
02	Ammonium Acetate	GR/AR
03	Methyl tertiary butyl ether (MTBE)	HPLC
04	Water	HPLC (or) Milli Q

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