Desvenlafaxine: a new antidepressant

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Desvenlafaxine, a synthetic form of the major active metabolite of venlafaxine, is a new serotonin-noradrenaline reuptake inhibitor (SNRI) available for the treatment of major depressive disorder.

Major depressive disorder (MDD) is a significant and increasing cause of impairment and disability, impacting on the individual and his or her social interactions. In any given year, almost 800,000 adults in Australia will experience a depressive illness – the third most common cause of illness among women and the tenth most common cause among men. In 2003 to 2004, depression was the fourth most frequently managed problem by general practitioners in Australia.[1]

Despite improvements in treatment, depression remains an often chronic and recurring disorder with high rates of incomplete response to treatment.[2] Beginning with the introduction of venlafaxine (Efexor-XR) in 1994, a new generation of antidepressants has emerged. These antidepressants have come to be classified as serotonin-noradrenaline reuptake inhibitors (SNRIs). Venlafaxine has been shown to be least as effective as selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression,[3] although some evidence suggests a moderate superiority in efficacy.[4,5]

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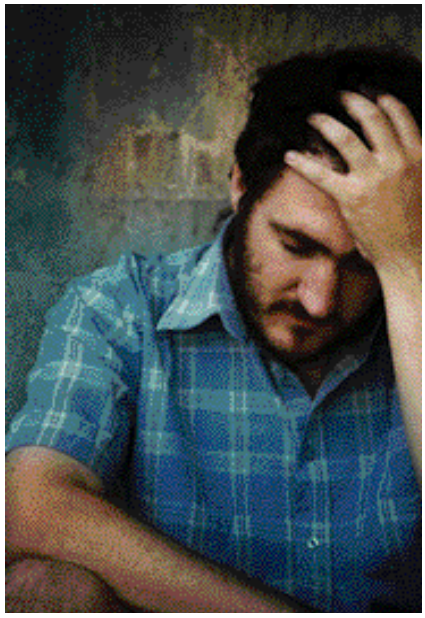
What is desvenlafaxine?

Desvenlafaxine (Pristiq) is the synthetic form of the major active metabolite of venlafaxine and demonstrates a similar pharmacodynamic and pharmacokinetic profile to its parent drug.[6] As with the other SNRIs, desvenlafaxine selectively inhibits the reuptake of serotonin and noradrenaline, leading to increased levels of these two key neurotransmitters in central neuronal synapses.

Desvenlafaxine is the third SNRI to become available in Australia and has been approved for the treatment of MDD and prevention of relapses in adults. It is available on the PBS (restricted benefit) for patients with MDD, in 50 mg and 100 mg tablets. Desvenlafaxine is also currently being investigated as a non-hormonal treatment for vasomotor symptoms associated with menopause, but has yet to receive approval for this indication.

How effective is desvenlafaxine?

The efficacy of desvenlafaxine in the treatment of MDD has been established in a number of placebo-controlled, randomised, double-blind studies of adult outpatients with MDD (n=1108). A meta-analysis of these trials showed a statistically significant decrease in the Hamilton Rating Scale for Depression 17-item total scores compared with placebo up to doses of 400 mg/day.[7] However, there was no evidence of a positive dose-response with daily dosing of greater than 50 mg.



The efficacy of desvenlafaxine in the prevention of relapse of depression compared with placebo has been demonstrated in two long-term studies.[8,9] At present, no studies have been published comparing desvenlafaxine and an active comparator, including no direct comparison between desvenlafaxine and venlafaxine in MDD.

Starting treatment and dosage regimen

Desvenlafaxine is delivered as desvenlafaxine succinate in a sustained-release formulation for once-a-day oral administration. It is available as 50 and 100 mg tablets. The current recommended starting dose is 50 mg once daily with or without food. If dose increases are required, they should be made gradually and at intervals of a minimum of seven days at a time (i.e. increase the daily dose by 50 mg for at least seven days before increasing the dose any further). The maximum recommended daily dose is 200 mg/day.

Dosing every other day is recommended in patients with severe renal impairment (creatinine clearance <30 mL/min). In patients over 75 years of age there are no specific dosing recommendations, although close monitoring is suggested.

continued

Adverse reactions

The safety and tolerability of desvenlafaxine is comparable to that of the other SNRIs.[10] The major treatment-emergent adverse events associated with its use include: nausea, dry mouth, hyperhidrosis, insomnia, fatigue, headache, blurry vision, sexual dysfunction, dizziness and constipation.[11] Of these, nausea (reported by 17 to 50% of patients receiving desvenlafaxine 50 mg/day to 400 mg/day) and dizziness (7 to 19% of patients receiving 50 mg/day to 400 mg/day) are the most common adverse events in the short term. The corresponding rates for patients receiving placebo in these trials were 8 to 11% for nausea and 2 to 12% for dizziness.[6] In longer term treatment, vomiting is the most common event. Discontinuation rates due to adverse events are dose dependent: at 50 mg/day dosing, desvenlafaxine is well tolerated with a rate of discontinuation similar to that of placebo (4%). For doses of 400 mg/day, the discontinuation rate increases to 18%.[7]

Small but statistically significant mean increases in blood pressure and heart rate have been observed in clinical trials. In one study clinically important changes in blood pressure were noted in a small number of patients. It is recommended to monitor blood pressure in patients receiving desvenlafaxine. On the other hand, no patients had clinically relevant changes in QTc interval or body weight.

As with all available antidepressants, concerns have been raised regarding the potential for suicide. In all the reported studies conducted using desvenlafaxine, there have been 10 instances of suicidal attempts or intent, with one reported death. As with other antidepressants, all patients should be monitored for these behaviours, particularly in the early stages of treatment.

Contraindications

Hypersensitivity to desvenlafaxine or venlafaxine is the main contraindications to the use of desvenlafaxine. It should also not be used in conjunction with other antidepressants (e.g. SSRIs, monoamine oxidase inhibitors [MAOIs] or other SNRIs) or serotonergic agonists (e.g. St John's wort, tramadol) due to the risk of serotonin syndrome, a potentially life-threatening condition. It is not approved for use in paediatric populations.

Precautions

If a patient's treatment is being switched to desvenlafaxine from a MAOI, a minimum 14-day washout period is required. If treatment is switched to a MAOI from desvenlafaxine, a minimum seven-day drug-free period is needed.

When desvenlafaxine is to be discontinued, the dose should be tapered over a two- to three-week period to avoid discontinuation emergent symptoms.

Activation of mania/hypomania can occur in a small percentage of patients with mood disorders treated with antidepressants. As such, desvenlafaxine should be used cautiously in patients with a history of mania or hypomania.

No studies have been performed investigating the efficacy or safety of desvenlafaxine in pregnancy. Currently desvenlafaxine is classified as a pregnancy category B2 drug. It is excreted in breast milk, which may result in adverse events in infants who are breast-fed. Recently concerns have been raised regarding women taking SSRIs or SNRIs late in the third trimester of pregnancy and the potential for respiratory complications, prolonged hospitalisation and serotonin withdrawal syndrome in their neonates. Consideration of the risk and benefits of desvenlafaxine use should, therefore, occur in all pregnant women prior to the initiation of treatment.

Safety in overdose

Little information is available regarding the safety of desvenlafaxine in overdose. In the premarketing clinical trials no cases of fatal overdose of desvenlafaxine were noted. The management of overdose should involve of the general supportive and symptomatic measures used in the treatment of overdose of any SSRI or SNRI.

Drug–drug interactions

Desvenlafaxine has minimal impact on the cytochrome P450 system, which is responsible for metabolising up to 25% of pharmaceutical agents. This might be a clinical advantage in patients receiving other medications metabolised by this system.

As mentioned above, desvenlafaxine should not be used concomitantly with medications that affect serotonin levels.

Summary

- The available research supports the efficacy, safety and tolerability of desvenlafaxine in the treatment of MDD, including the prevention of relapses.
- The efficacy of desvenlafaxine does not appear related to dosage, whereas tolerability of the drug is dose dependent.
- Desvenlafaxine may have particular benefit in the medically unwell due to its pharmacokinetic profile and in patients with MDD and comorbid vasomotor symptoms associated with menopause.
- The place of desvenlafaxine in the treatment of depression is yet to be established due to a lack of clinical research, in particular direct comparisons with available antidepressants. MT

References

A list of references is available on request to the editorial office.

COMPETING INTERESTS: Dr Bochsler: None. Dr Olver has received educational and research grants from AstraZeneca, Eli Lilly and Janssen-Cilag in the past five years. Professor Norman has served on advisory boards and/or received support for travel, talks or research from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Lundbeck, Organon, Pfizer, Servier and Wyeth in the past five years.

Medicine Today 2010; 11(1):45-46

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