Desvenlafaxine Recommendations Report

Meeting objectives

- Obtain insights from an international panel of experts on the best way to position desvenlafaxine (DES) as an alternative for treating depression, which patient profiles can most benefit from its use, and other practical recommendations that may be useful for clinicians.
- Develop and circulate a report detailing key recommendations from the expert panel to guide the use of DES in clinical practice.
- Ultimately improve the quality of care for patients who need treatment with antidepressants.

Advisors

Dr Javier De Diego Adeliño
Psychiatrist, Hospital de la Santa Creu i Sant Pau and Associate Professor of Psychiatry of Universitat Autònoma de Barcelona, Barcelona, Spain

Prof Dr Mazda Adli
Professor for Psychiatry and Chair of Fliedner Klinik, Centre for Psychiatry, Psychotherapy and Psychosomatic Medicine Charité-University Medicine, Berlin, Germany

Dr Antonio Lains
Director of Neuroscience and Mental Health Clinic, Hospital Cruz Vermelha, Lisbon, Portugal

Prof Dr Claudia Carmassi
Associate Professor of Psychiatry, Psychiatric Clinic, University of Pisa Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy

Introduction

The Desvenlafaxine Recommendations Report Meeting was held in Frankfurt on 19 May 2023. The event was hosted by representatives of Neuraxpharm, who posed open questions about the real-world clinical use of DES but did not otherwise influence the meeting content. The overall aim was to collect information from experts in psychiatry about how DES can be used effectively in the management of depression. In particular, discussions focused on how DES differs from its parent compound venlafaxine (VEN) when used in the clinic. The insights gained will be used to provide educational content to help clinicians across Europe use DES effectively and appropriately.

The advisors present at the meeting had practical experience of prescribing DES to patients and openly shared their experiences during the discussions.

Please note that the contents of this report represent the experiences and opinions only of the individuals present at the meeting.

Patient profile: Who can benefit the most from using SNRIs, particularly DES?

What features does it have for specific symptomatology?

The overall patient profile for DES comprises several sub-populations of patients with major depressive disorder (MDD). Based on the advisors' clinician experiences, some of the patient populations in whom DES may be considered as a 1L or 2L SNRI include:

- Young, treatment naïve patients
- Patients with moderate to severe depression characterised by apathy, low motivation, anhedonia, and/or psychomotor inhibition or patients maintaining any of these residual symptoms after failures with other previous antidepressants
- Patients with multimorbidity and resulting polypharmacy
- Patients who are perimenopausal and experiencing vasomotor symptoms
- Patients who exhibit substance or alcohol abuse
- Other patients who are likely to have impaired liver function and/or increased risk of drug-drug interactions (HIV, cancer, etc)

In addition, DES may be considered as a 2L treatment for patients with MDD who are also elderly and/or have hypertension. Different features of DES are relevant to each of these sub-populations:

- **Elderly:** First-pass metabolism of drugs decreases with age. Furthermore, elderly people are more likely to be polymedicated. Due to its minimal hepatic metabolism, DES may be a first choice in these patients when considering an SNRI.
- **Hypertension:** The risk of high BP may be lower with DES than with other SNRIs. A study assessing MDD with DES 50 mg/day, confirmed no significant changes in BP over 11 months of treatment (Rosenthal 2013).

Relevance of DES features to sub-populations of patients with MDD

- **Dual-acting efficacy even at low doses:** The noradrenergic effect, which can be achieved with 50mg/day, is important for MDD patients who exhibit symptoms like abulia, fatigue and lack of motivation.
- **Minimal drug–drug interactions:** DES has minimal metabolism mediated by major cytochrome P450 enzyme systems and therefore has a low incidence of drug-drug interactions (Kamath 2008; Kornstein 2014;). DES efficacy is not diminished in patients with comorbidities including metabolic syndrome (McIntyre 2016), or in patients taking concomitant medications, including tamoxifen (Nichols 2014). DES is, therefore, a good treatment option for patients who are elderly, comorbid, etc; any patients likely to receive treatments for other health conditions.
- **Generally good tolerability profile:** DES has a low risk of acute and long-term side effects (Kornstein 2014), including weight gain, compared with other antidepressants. In addition, although DES treatment may not be completely free of sexual adverse effects, it produces sexual dysfunction to a lesser degree than VEN and other antidepressants (Clayton 2009; Tourian 2010; Montejo 2019). It is, therefore, a good option for patients

who place a high value on avoiding such side effects of antidepressant treatment, such as young people.

- **Simple dosing:** DES is initiated at a dose of 50 mg once daily, which is already therapeutic, and it can easily be adjusted to higher doses such as 100, 150 or 200 mg if necessary (Boyer 2015; Faxilex/Fasilex/Desveneurax® SmPC). This simple dosing schedule can promote treatment adherence and is particularly suitable for patients with potential adherence issues like the elderly and those with cognitive impairment.

GP vs psychiatry: Considerations of use

Patients with mild to moderate depression are often managed in a primary care setting, while patients with more complex depression are usually referred to specialists in secondary care. However, the drastic rise in the prevalence of mental disorders over the last decade, dramatically exacerbated by the COVID-19 pandemic (COVID-19 Mental Disorders Collaboration, 2021), has led to overburdened healthcare systems. Waiting times for psychiatry consultations have been increasing across Europe. As such, even if the total number of patients being referred to specialist care has been increasing, the proportion of patients with depression and anxiety disorders who are not referred and are treated in the primary care setting is greatly increasing. Some GPs have an interest in managing patients with depression but are limited by very short patient consultations, during which they must also attend to the patient's other medical needs. Therefore, they need antidepressant treatment options that allow straightforward management of depression.

Treatment in primary care typically begins with an SSRI rather than with dual-acting antidepressants. GPs may be reluctant to consider dual-acting agents due to concerns over tolerability or lack of experience, but the good safety profile of DES means that it may be considered even as a 1L option in primary care.

The safety profile of the different antidepressant options is an important factor in clinical decision-making (Kennedy 2016). Overall, treatment decisions must be made with long-term goals in mind, including the long-term risks and possible impact of side effects of therapy, as well as the approach to stopping therapy, should it lead to complete symptom remission. In this regard, DES is an attractive treatment option because of the low risk of long-term side effects (Tourian 2010; Kornstein 2014).

In addition, the high prevalence of multimorbidity in patients with MDD means that antidepressants must be well tolerated alongside a multitude of other medications (Read 2017; Wiersema 2022; Ghaed-Sharaf 2022). Prescribers must consider whether dose optimisation will be needed when starting antidepressant medication; again, the simple once-daily dosing of DES is an advantage in this setting.

The dual action and good tolerability profile of DES may encourage GPs and specialists to prescribe it for eligible patients, using an SNRI earlier in the treatment pathway than they would consider if DES were not available.

Should DES be an alternative to VEN, and why?

There is a lack of clarity over the efficacy of VEN and DES at equivalent doses, owing to a lack of supporting evidence. An indirect comparison of VEN and DES found DES to be non-inferior to VEN in terms of efficacy (Coleman 2012). Studies show that DES exhibits dual action on serotonin and norepinephrine pathways throughout its entire dose range (Deecher 2006), but the dual efficacy of VEN is not observed consistently, especially at doses below 225 mg (Debonnel 2007; Kamath 2008). This is an important consideration when treating patients whose symptoms need to be addressed by both serotonergic and noradrenergic activity.

Clinician experience further supports that the efficacy of DES at lower doses (50–100 mg) promotes a beneficial balance of dual effectiveness, allowing patients to benefit from the full spectrum of its dual efficacy and low risk of side effects. Higher doses of VEN are required to achieve similar dual effects, which comes with the added risk of other side effects. The potential for drug–drug interactions with VEN can also be a concern and a barrier to prescribing it, particularly in patients with comorbidities. The absence of relevant hepatic metabolism of DES represents an added benefit for patients who may engage in substance and alcohol abuse.

Despite ongoing questions over efficacy, DES offers clear benefits over VEN in terms of simplicity of dosing, and lower risk of side effects (Carrasco 2016). The advisors described

where switching from VEN to DES may offer potential benefits. For example, a hypothetical patient with residual symptoms or side effects following treatment with high-dose VEN, who is also receiving medications for several comorbidities, may benefit from switching from VEN to lower-dose DES. The psychiatrist's goals must be pragmatic – even if full remission of symptoms is unlikely in certain patients, they may benefit from the better tolerability of DES compared with high-dose VEN. The advisors added a note of caution about switching antidepressants, noting that short-term side effects may result from withdrawal of the original drug rather than the newly introduced one.

Pharmacokinetic factors

Unlike with DES, the effectiveness of VEN is influenced by patient metabolism. Studies have demonstrated the effects of cytochrome P450 genetic polymorphisms on the variability in pharmacokinetics of VEN and DES (Preskorn 2009; Lobello 2010; Nichols 2011; Zanger 2013). Plasma levels of key metabolites are significantly lower in the 'poor P450 2D6 metabolizer' phenotype compared with 'extensive P450 2D6 metabolizers' following VEN administration. This translates into variable efficacy with VEN depending on the patient's metabolic phenotype (Lobello 2010). In contrast, the pharmacokinetics of DES are more reliable across metabolic phenotypes because DES metabolism is minimally mediated by P450 enzymes (Preskorn 2009). This is another feature that contributed to the advisors' perception of DES as a straightforward, easy-to-use antidepressant.

Side effects

Studies support a low incidence of sexual dysfunction with DES treatment (Clayton 2015; Montejo 2019), although the advisors agreed that a better understanding of this side effect requires study in long-term trials. Patients are concerned about the risk of sexual dysfunction as a possible side effect of antidepressant treatment, and their concern increases as their depression symptoms improve. In the real world, the impact of DES on sexual function is complex, and depends on whether the dysfunction existed prior to treatment as a symptom of depression, or if it develops following treatment initiation. In fact, some patients who present with sexual dysfunction prior to treatment initiation report improvement in their sexual function after treatment with DES (Clayton 2015). Nevertheless, the advisors agreed that DES has a lower risk of sexual dysfunction compared with VEN.

For many patients with MDD, the fear of weight gain is more significant than the fear of sexual dysfunction. A clear benefit of DES is the low risk of weight gain among patients receiving this treatment (Tourian 2010; McIntyre 2015).

Hypertension is also a concern for clinicians when making treatment decisions. There is a dose-dependent increase in blood pressure (BP) in patients receiving DES after short-term treatment, but risk of new onset hypertension is generally low (Rosenthal 2013; Thase 2015).

DES positioning

DES can be considered a good option for use in primary care because it is easy for GPs to manage, due to its simple dosing and good tolerability profile. It can be a valid treatment option in 1L as an alternative to SSRIs, especially in moderate to severe depression, where greater efficacy is needed than SSRIs can offer. It may be used in later lines of treatment for treatment-resistant depression.

DES may also be considered a good alternative to duloxetine in countries where this product is used. Duloxetine is indicated for MDD and can be also used for diabetic peripheral neuropathic pain or generalised anxiety disorder. Although it has not received a formal approval, there are some data supporting the effectiveness of DES in patients with neuropathic pain or MDD associated with painful symptoms (Allen 2014).

Switching antidepressants

Prescribers must consider the optimal strategy for changing a patient's medication, moving from the 1L antidepressant to a different treatment. A washout/tapering period of the first antidepressant can be considered, although this introduces the risk of leaving the patient untreated. The reason for switching treatments is probably because the patient is already having issues, so a tapering approach introduces a risk of their symptoms worsening. If avoiding worsening of symptoms is a priority, a cross-switch strategy should be considered.

Practical recommendations for clinicians when using DES

Dosage

The prescribed dosage of DES is likely to differ in patients treated in GP versus specialist settings. The recommended dose of 50 mg once-daily is commonly prescribed for mild to moderate depression. The advisors appreciate the simplicity of being able to initiate treatment at the therapeutic dose, without concern over side effects. More complex cases are typically managed by psychiatrists in secondary care, where doses of 50–100 mg are commonly prescribed, increasing to 200 mg for certain patients.

Despite published evidence indicating that increasing the doses above 50 mg/day does not clearly correlate with an increase in efficacy, clinical experience supports the benefits of using DES doses exceeding 50 mg in real-world patients with moderate to severe MDD. Clinical experience suggests that higher doses of DES can have additive effects, without a relevant increase in risk of side effects; the advisors agreed that while 50 mg is the approved starting therapeutic dose, some patients appear to experience increased efficacy at higher doses. For example, a dose increase may be beneficial for a patient whose symptoms have improved but who still exhibits residual symptoms of depression without reporting side effects of DES. Another example might be in patients who experience ongoing symptoms despite receiving other previous lines of therapy – in this case, it may not be advisable to start with 50 mg of DES, but rather try gradually increasing the dose of DES up to at least 100 mg and assess closely for increased efficacy and tolerability. The advisors commented that there is a need for more data to reinforce their clinical experience in this regard, to better inform decision-making. Therapeutic serum levels are unknown and may not be representative of therapeutic efficacy.

No studies have been conducted in treatment-resistant depression. A major goal of treatment is to avoid chronic, ongoing symptoms of depression; the likelihood of good treatment outcomes diminishes as the duration of unmanaged symptoms increases

(Diego-Adeliño J 2010). For this reason, the efficacy of any antidepressant must be assessed regularly; every 4–6 weeks is advisable. A lack of response to DES soon after treatment initiation suggests a poor longer-term outcome (Katzman 2017), and should prompt the clinician to consider increasing the DES dose. Such an approach allows treatment optimisation and avoids chronic symptomology. Treatment algorithms help to prevent patients from staying on ineffective treatments for too long.

The advisors welcomed the possibility of 150 mg and/or 200 mg DES formulations, which would facilitate DES dose adjustments. Patients may also welcome these higher dose formulations, as they can increase their dose while still taking one tablet daily.

Assessing treatment effectiveness

A major challenge of using antidepressants is measuring their efficacy objectively in clinical settings. The advisors highlighted the need to develop more objective clinical measures of antidepressant efficacy. Symptoms like cognitive impairment are currently often assessed subjectively rather than objectively, which can be misleading and situational; patients' perceptions of their symptoms change throughout their treatment as their depression improves and they become more functional. The advisors cited a lack of data showing effects of DES on cognitive impairment in depression and agreed on the difficulty in assessing this parameter objectively, especially in primary care.

However, routinely employing easy-to-use symptom rating scales such as the PHQ-9 can help primary care doctors assess treatment response, guide further treatment adjustments, and greatly improve treatment outcomes (Guo 2015).

Managing treatment withdrawal

When complete remission has been established for a long time, it is common to consider withdrawal of treatment. Withdrawal symptoms are typically transient and harmless, and patients benefit from education so they understand the types of withdrawal symptoms they may encounter, and how to manage them if they are bothersome. Abrupt cessation of DES treatment is not advisable, to help avoid withdrawal symptoms. Discontinuation symptoms of DES may be felt more quickly than with other antidepressants, e.g. fluoxetine. Patients often become concerned at the thought of stopping an effective therapy, which leads to further worry when they experience withdrawal symptoms.

Prior to initiating treatment, prescribers should have an open discussion with their patients, where they inform them about potential side effects and the possibility of withdrawal symptoms emerging. This will help manage patients' expectations and avoid anxiety during the discontinuation period. Should patients raise any concerns with regards to withdrawal symptoms, the prescribing physician may reassure them and provide further information. More specifically, some patients may benefit from being informed that 1) withdrawal symptoms are usually mild, and even if unpleasant, they are generally benign;

2) experiencing withdrawal symptoms is not the same as having an addiction or being dependent on a medication, nor does it mean that the patient is suffering from a relapse;

3) there are several strategies to taper off the medication that can prevent withdrawal symptoms from emerging.

Some patients may be more prone to suffering withdrawal symptoms than others. During treatment, doctors may ask their patients if they inadvertently skipped a dose and, if so, whether they experienced any discomfort. This may be indicative of the patient's susceptibility to withdrawal symptoms. Treatment duration also has a direct correlation with the likelihood of antidepressant withdrawal symptoms – a longer treatment duration is associated with a high risk of negative effects during discontinuation. Therefore, a cautious approach to treatment cessation is advised for patients who are highly likely to experience withdrawal symptoms. The clinician may employ techniques such as, 1) lowering DES dosage to 50 mg every other day as a bridge to complete treatment withdrawal; 2) staying on each dosing step for as long as needed until the patient is no longer experiencing any discomfort; 3) in rare cases where the prior strategies fail, temporarily adding fluoxetine to the regimen while discontinuing DES, and later discontinuing fluoxetine.

While the withdrawal period may be longer when using a cautious approach, there is an overall benefit that the patient feels in control.

Conclusions

In summary, the advisors highlighted several specific patient populations and clinical settings in which DES can be used effectively to optimise management of MDD. There is a need for improved awareness and education on how DES can be used effectively, especially in primary care.

References

Allen R, Sharma U, Barlas S. Clinical experience with desvenlafaxine in treatment of pain associated with diabetic peripheral neuropathy. J Pain Res. 2014;7:339–51.

Boyer P, Vialet C, Hwang E, et al. Efficacy of desvenlafaxine 50 mg/d versus placebo in the long-term treatment of major depressive disorder: a randomized, double-blind trial. Prim Care Companion CNS Disord. 2015;17(4):10.4088/PCC.14m01711.

Carrasco JL, Kornstein SG, McIntyre RS, et al. An integrated analysis of the efficacy and safety of desvenlafaxine in the treatment of major depressive disorder. Int Clin Psychopharmacol. 2016; 1(3):134–46.

Clayton AH, Hwang E, Kornstein SG, et al. Effects of 50 and 100 mg desvenlafaxine versus placebo on sexual function in patients with major depressive disorder: a meta-analysis. Int Clin Psychopharmacol. 2015;30(6):307–15.

Clayton AH, Kornstein SG, Rosas G, et al. An integrated analysis of the safety and tolerability of desvenlafaxine compared with placebo in the treatment of major depressive disorder. CNS Spectr. 2009;14(4):183–95.

Coleman KA, Xavier VY, Palmer TL, et al. An indirect comparison of the efficacy and safety of desvenlafaxine and venlafaxine using placebo as the common comparator. CNS Spectr. 2012; 17(3):131–41.

COVID-19 Mental Disorders Collaborators. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet. 2021 6;398(10312):1700–12.

Debonnel G, Saint-André E, Hébert C, et al. Differential physiological effects of a low dose and high doses of venlafaxine in major depression. Int J Neuropsychopharmacol. 2007;10(1):51–61.

Deecher DC, Beyer CE, Johnston G, et al. Desvenlafaxine succinate: A new serotonin and norepinephrine reuptake inhibitor. J Pharmacol Exp Ther. 2006;318(2):657–65.

Diego-Adeliño J, et al. A short duration of untreated illness (DUI) improves response outcomes in first-depressive episodes. J Affect Disord. 2010;120(1-3):221–5.

Faxilex/Desveneurax/Fasilex® Summary of Product Characteristics.

Ghaed-Sharaf M, Hariri S, Poustchi H, et al. The pattern of medication use, and determinants of the prevalence of polypharmacy among patients with a recent history of depressive disorder: results from the pars cohort study. BMC Psychol. 2022;10:12.

Kamath J, Handratta V. Desvenlafaxine succinate for major depressive disorder: a critical review of the evidence. Expert Rev Neurother. 2008;8(12):1787–97.

Katzman MA, Nierenberg AA, Wajsbrot DB, et al. Speed of improvement in symptoms of depression with desvenlafaxine 50 mg and 100 mg compared with placebo in patients with major depressive disorder. J Clin Psychopharmacol. 2017;37(5):555–61.

Kennedy SH, Lam RW, McIntyre RS, et al; CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments. Can J Psychiatry. 2016;61(9):540-60. Erratum in: Can J Psychiatry. 2017;62(5):356.

Kornstein SG, McIntyre RS, Thase ME, et al. Desvenlafaxine for the treatment of major depressive disorder. Expert Opin Pharmacother. 2014;15(10):1449–63.

Lobello KW, Preskorn SH, Guico-Pabia CJ, et al. Cytochrome P450 2D6 phenotype predicts antidepressant efficacy of venlafaxine: a secondary analysis of 4 studies in major depressive disorder. J Clin Psychiatry. 2010;71(11):1482–87.

Liebowitz MR, Tourian KA. Efficacy, safety, and tolerability of desvenlafaxine 50 mg/d for the treatment of major depressive disorder: a systematic review of clinical trials. Prim Care Companion J Clin Psychiatry. 2010;12(3):PCC.09r00845.

McIntyre RS, Fayyad RS, Guico-Pabia CJ, et al. A post hoc analysis of the effect of weight on efficacy in depressed patients treated with desvenlafaxine 50 mg/d and 100 mg/d. Prim Care Companion CNS Disord. 2015;17(3):10.4088/PCC.14m01741.

McIntyre RS, Fayyad R, Mackell JA, et al. Effect of metabolic syndrome and thyroid hormone on efficacy of desvenlafaxine 50 and 100 mg/d in major depressive disorder. Curr Med Res Opin. 2016;32(3):587–99.

Montejo AL, Becker J, Bueno G, et al. Frequency of sexual dysfunction in patients treated with desvenlafaxine: A prospective naturalistic study. J Clin Med. 2019;8(5):719.

Nichols AI, Lubaczewski S, Liang Y, et al. Open-label, 2-period sequential drug interaction study to evaluate the effect of a 100-mg dose of desvenlafaxine on the pharmacokinetics of tamoxifen when coadministered in healthy postmenopausal female subjects. Int J Clin Pharmacol Ther. 2014;52(10):830–41.

Nichols AI, Focht K, Jiang Q, et al. Pharmacokinetics of venlafaxine extended release 75 mg and desvenlafaxine 50 mg in healthy CYP2D6 extensive and poor metabolizers. Clin Drug Investig. 2011;31(3):155–67.

Preskorn S, Patroneva A, Silman H, et al. Comparison of the pharmacokinetics of venlafaxine extended release and desvenlafaxine in extensive and poor cytochrome P450 2D6 metabolizers. J Clin Psychopharmacol. 2009;29:39–43.

Read JR, Sharpe L, Modini M, et al. Multimorbidity and depression: A systemic review and meta-analysis. J Affect Disord. 2017;221:36–46.

Rosenthal JZ, Boyer P, Vialet C, et al. Efficacy and safety of desvenlafaxine 50 mg/d for prevention of relapse in major depressive disorder: a randomized controlled trial. J Clin Psychiatry. 2013;74(2):158–66.

Thase ME, Fayyad R, Cheng RF, et al. Effects of desvenlafaxine on blood pressure in patients treated for major depressive disorder: a pooled analysis. Curr Med Res Opin. 2015;31(4):809–20.

Tourian KA, Leurent C, Graepel J, et al. Desvenlafaxine and weight change in major depressive disorder. Prim Care Companion J Clin Psychiatry. 2010;12(1):PCC.08m00746.

Wiersema C, Oude Voshaar RC, van den Brink RHS, et al. Determinants and consequences of polypharmacy in patients with a depressive disorder in later life. Acta Psychiatr Scand. 2022; 146(1):85–97.

Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacol Ther. 2013;138(1):103–41.

