MMG004 GUIDELINES FOR THE USE OF HIGH DOSE VENLAFAXINE AND THE COMBINATION OF VENLAFAXINE AND MIRTAZAPINE IN THE TREATMENT OF DEPRESSION
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Why we need this Guideline
The majority of patients with depression can be treated with a single antidepressant agent within licensed doses. However there may be a small proportion of patients with treatment resistant depression where using above licensed doses of venlafaxine or a combination of mirtazapine and venlafaxine may be effective / beneficial.

What the Guideline is trying to do
To provide guidance on the use of high dose venlafaxine and the combination of venlafaxine and mirtazapine in the treatment of depression.

Which stakeholders have been involved in the creation of this Guideline
NHFT Medicines Management Committee

Any required definitions/explanations
BP - blood pressure
ECG - electrocardiogram
NHFT - Northamptonshire Healthcare NHS Foundation Trust
SmPC - Summary of Product Characteristics

Key duties

Medicines Management Committee
Will approve and review these guidelines

Medical Director
Is responsible for the dissemination of this guideline to their Clinical Directors and Clinical Tutors

Clinical Directors
Are responsible for the dissemination and implementation of the guideline in their service areas

Heads of Service/hospitals
Are responsible for the dissemination and implementation of the guideline in their service areas

Doctors
Are responsible for reviewing the patient and ensuring that the:

- Rationale for use of high dose venlafaxine is documented on SystmOne along with the details of BP and ECG monitoring.
When it is necessary to use the combination of venlafaxine and mirtazapine, clinicians must explain and document the rationale for such prescribing and specify any monitoring requirements to nursing staff as well as pass this information on when asking GPs to take over prescribing.

**Prescribing guidelines**

**High dose venlafaxine**

The Summary of Product Characteristics (SmPC) for both sustained release (XL) and regular release venlafaxine now states a maximum daily dose of 375mg (an increase for the XL preparation from 225mg).¹

The prescribing of high dose venlafaxine is not a regular occurrence within the Trust.

There is limited available evidence for use of venlafaxine above licensed dosage. There are only a small number of studies:

- One is an open label naturalistic case study of 5 patients (4 patients received 450mg and 1 patient’s dose was increased to 600mg during the study). All of these patients fit the criteria for treatment resistant depression but there was no conclusive evidence that using doses above 375mg had additional benefits as the patients were taking a combination of other psychotropic medications.²

- Another study by Harrison et al looked at the tolerability of high dose venlafaxine. It did not focus on efficacy. 35 patients received doses ranging from 375mg-600mg a day and 35 patients received low dose <375mg. Side effects were reported to be more significant in the high dose group. The authors concluded that this demonstrated tolerability of doses up to 600mg but the numbers were small and rare side effects would have been missed.³

As these studies are small, they provide little support for routine use of doses above 375mg.

**Practice points for Venlafaxine prescribing:**

Because of the risk of dose-related adverse effects, dose increments should be made only after a clinical evaluation. The lowest effective dose should be maintained.¹

Dosage increases can be made at intervals of two weeks or more. If clinically warranted, due to symptom severity, doses can be increased at more frequent intervals, however no less than 4 days.¹, ⁴

For patients prescribed venlafaxine, blood pressure should be checked on initiation and regularly during treatment, particularly before and after dose titration/changes. For patients who experience a sustained increase in blood pressure, the dose should be reduced or discontinuation considered.¹, ⁵

**Pre-existing hypertension must be controlled before prescribing venlafaxine,** whether at high dose or not, and clinicians must ensure that hypertension is well controlled and blood pressure is monitored throughout treatment.¹
The United Kingdom Medicines and Healthcare products Regulatory Agency (UK MHRA), recommends that doses above 300mg should only be prescribed under the supervision of or advice of a specialist.\(^5\)

**When high dose venlafaxine is prescribed (doses above 375mg) details of ECG monitoring and BP monitoring should be documented on SystmOne and it should also be documented that the prescriber has discussed the regime with the patient and the patient’s consent has been obtained to take high dose treatment.**

If a GP is requested to continue prescribing high dose venlafaxine, details of the rationale for prescribing the high dose must be provided to the GP. Results of any investigations already undertaken e.g. ECGs and blood pressure must be shared with the GP along with details of any continued monitoring requirements, which should include frequency of ECG and BP monitoring as dictated by the clinical presentation of the individual.

**Venlafaxine and mirtazapine combinations**

**Theoretical basis for combination:**

- Venlafaxine and its active metabolite inhibit synaptosomal reuptake of serotonin, noradrenaline and to a lesser extent dopamine to produce their antidepressant effect.
- Mirtazapine is a centrally active pre-synaptic alpha\(_2\)-antagonist, which increases central noradrenergic and serotonergic neurotransmission.

Noradrenaline neurotransmission is partly under the control of presynaptic alpha\(_2\)-adrenergic autoreceptors which, when stimulated by noradrenaline, inhibit the release of noradrenaline into the synapse. There are other alpha\(_2\)-receptors (heteroreceptors) located on the presynaptic terminal end of serotonergic neurons which, when stimulated by noradrenaline, inhibit the release of serotonin. Blockade of these receptors would prevent this inhibition.

It is thought that mirtazapine enhances noradrenaline and serotonin transmission by blockade of these receptors thus the augmentation of venlafaxine with mirtazapine results in a synergistic effect on serotonergic systems.

Again the evidence for this combination is limited.

There are 2 small studies that look at mirtazapine augmentation with venlafaxine (there are other studies which focus on combinations of mirtazapine and paroxetine, citalopram and lithium).

One open label study by Carpenter et al looked at 20 patients on antidepressant therapy who received mirtazapine augmentation.\(^7\) 6 patients were taking venlafaxine.
One patient was on venlafaxine 100mg, two patients were taking venlafaxine 150mg, one patient was taking venlafaxine 200mg, one was taking venlafaxine 75mg and desipramine 200mg and one was taking venlafaxine 300mg and fluoxetine 60mg.

They had been taking these primary medications for at least four weeks at the highest tolerable dose for them and were classified within the study as treatment refractory. All patients were commenced on mirtazapine 15-30mg every night. From the information in the paper it is not clear which patients received which dose of mirtazapine although the majority of patients in the study (90%) commenced on 15mg and were maintained on this dose. Only 3 of the 6 patients on venlafaxine were classed as responders at the end of 4 weeks.

A placebo-controlled trial in 26 patients by Carpenter et al looked at augmentation of antidepressant therapy. Of the 26 patients 3 patients were taking venlafaxine as their primary antidepressant and only 1 was in the mirtazapine group.

Between 2002 and 2005 Hannan et al reviewed 32 patients with persistent depressive illness that received a combination of venlafaxine and mirtazapine at some point during the 3 year period. At a 6 month review 18 patients (56%) had significantly responded. Clinical response was found typically to have occurred at moderate and high dose treatment with both agents.

With such small numbers, little can be concluded from these studies. However the combination of venlafaxine and mirtazapine is recommended as a treatment option for treatment refractory depression in The Maudsley Prescribing Guidelines in Psychiatry.

Practice points when prescribing the combination of venlafaxine and mirtazapine:
When reviewing medication in patients who have not responded adequately to initial pharmacological interventions:

- Check adherence to initial treatment and whether any non-adherence is due to side effects
- Consider reintroducing previous treatments that have been inadequately adhered to and consider an increase in dose
- Consider switching to an alternative antidepressant

Whilst NICE Clinical Guideline (CG90) discusses the augmentation of antidepressants it does not specifically mention the combination of venlafaxine and mirtazapine and recommends that when considering combining antidepressants, other than mirtazapine or mianserin and an SSRI, that the adequacy of previous treatment should be reviewed before proceeding.

When using combinations of medicines (this should only normally be started in primary care in consultation with a consultant psychiatrist)

- Use medications that are known to be safe when used together
- Be aware of the increased side effect burden the combination may cause.
- Ensure all the patients physical medicines are reviewed and that the patient hasn’t been prescribed any other medication by their GP that acts on the serotonergic receptors e.g. triptans
When it is necessary to use the combination of venlafaxine and mirtazapine, clinicians must explain the rationale for such prescribing and any monitoring necessary for an individual patient when asking GPs to take over prescribing. The GP should be made aware that using combinations of serotonergic antidepressants increase the risk of developing serotonin syndrome which can be fatal.

Where the patient is routinely prescribed any physical medicines that act on the serotonin system e.g. triptans a discussion should occur between the prescriber and the GP to ensure that these meds are reviewed.

Serotonin syndrome is a potentially fatal adverse reaction that is attributed to a toxic hyper-serotonergic state from hyper-stimulation of the brain stem and 5HT1A and 5HT2 receptors. Onset is usually within a few hours of drug initiation or dose changes, and usually resolves in about 24 hours following discontinuation of all serotonergic drugs.

Symptoms of serotonin syndrome include and are usually a combination of at least three of the following:

- Mental state changes e.g. confusion, poor co-ordination, hypomania
- Agitation/Restlessness
- Tremor
- Sweating, fever, shivering
- Gastro intestinal side effects e.g. diarrhoea
- Hypertension
- Tachycardia
- Convulsions

Ensure all other causes have been ruled out such as infection, metabolic disturbances, substance misuse or withdrawal. 13

**Duloxetine in combination with other antidepressants:**

A literature search was carried out on the use of duloxetine in combination with other antidepressants. The results of this search showed very limited evidence for using this combination and therefore combinations should not be used except in exceptional circumstances. There is a possible risk of increased serotonergic effects when duloxetine is given with other drugs that affect serotonin levels as well interactions with a range of other antidepressants.4

**Training requirements associated with this Guideline**

**Mandatory Training**

There is no mandatory training associated with this Guideline.
Specific Training not covered by Mandatory Training
Not applicable to this document

How this Guideline will be monitored for compliance and effectiveness
There is no monitoring associated with this guideline.

Equality considerations
See MMP001 Control of Medicines Policy.

Reference Guide
1. Summary of Product Characteristics (Efexor) - accessed 19/09/2019
2. Mbaya P Safety and efficacy of high dose venlafaxine XL in treatment resistant major depression Hum Psychopharmacol Clin Exp 2002 17 335-339 (133112)
3. Harrison CL et al Tolerability of high dose venlafaxine in depressed patients Journal of Psychopharmacology 2004:18/2;200-20
4. British National Formulary Online via MedicinesComplete
5. UK MHRA. Updated prescribing advice for venlafaxine (Efexor/Efexor XL) 31st May 2006 – accessed 19/09/2019
### Document control details

<table>
<thead>
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**Guideline number:** MMG004

**Version control:** 1.2
APPENDIX 1 - Advice to GPs for patients discharged on high dose venlafaxine (total daily dose greater than 375mg)

High dose venlafaxine:

The Summary of Product Characteristics (SPC) for both sustained release (XL) and regular release venlafaxine now states a maximum daily dose of 375mg (an increase for the XL preparation from 225mg).¹

There is limited available evidence for use of venlafaxine above licensed dosage. There are only a small number of studies.

- One is an open label naturalistic case study of 5 patients, (4 patients received 450mg and 1 patient’s dose was increased to 600mg during the study). All of these patients fitted the criteria for treatment resistant depression but there was no conclusive evidence that using doses above 375mg had additional benefits as the patients were taking a combination of other psychotropic medications.²

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As these studies are small they provide little support for routine use of doses above 375mg.

The United Kingdom Medicines and Healthcare products Regulatory Agency (UK MHRA), recommends that doses above 300mg should only be prescribed under the supervision of or advice of a specialist.⁴

Interactions:

As with other serotonergic agents, the development of serotonin syndrome may occur with venlafaxine treatment, particularly with concomitant use of other serotonergic agents. Where the patient is routinely prescribed any physical medicines that act on the serotonin system e.g. triptans, tramadol, St John’s Wort, a discussion should occur between the prescriber and the GP to ensure that these medicines are reviewed.

Serotonin syndrome is a potentially dangerous adverse reaction that is attributed to a toxic hyper-serotonergic state from hyper-stimulation of the brain stem and 5HT1A and 5HT2 receptors. Onset is usually within a few hours of drug or dose changes.

Symptoms of serotonin syndrome include and are usually a combination of at least three of the following:

- Mental state changes e.g. confusion, poor co-ordination, hypomania
- Agitation/Restlessness
- Tremor
- Sweating, fever, shivering
• Gastro intestinal side effects e.g. diarrhoea
• Hypertension
• Tachycardia
• Convulsions

Ensure all other causes have been ruled out e.g. infection, metabolic disturbances, substance misuse or withdrawal.

Monitoring:

The Summary of Product Characteristics of Efexor (venlafaxine) states that all patients should be carefully screened for high blood pressure and pre-existing hypertension should be controlled before initiation of treatment. It also recommends that blood pressure should be reviewed periodically, after initiation of treatment and after each dose increase of venlafaxine.

However there are no guidelines available as to specific frequency of blood pressure monitoring nor is there guidance on specific actions to be taken if blood pressure increases. Locally a decision has been made that if there is an increase of greater than 10mm of mercury or BP reading is above 140 / 90 on two consecutive readings, advice should be sought from the consultant psychiatrist on treatment options. In all cases a risk/benefit discussion needs to take place with the patient, GP and Specialist to decide the safest option with regards to both mental and physical health. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or gradual discontinuation (over at least four weeks), or treatment of the elevated blood pressure as clinically indicated should be considered.

Patient specific monitoring will be detailed in the accompanying clinic letter.

References:

1. Summary of Product Characteristics (Efexor) - accessed 18/04/2011
2. Mbaya P Safety and efficacy of high dose venlafaxine XL in treatment resistant major depression Hum Psychopharmacol Clin Exp 2002 17 335-339 (133112)
3. Harrison CL et al Tolerability of high dose venlafaxine in depressed patients Journal of Psychopharmacology 2004:18/2;200-20
4. UK MHRA. Updated prescribing advice for venlafaxine (Efexor/Efexor XL) 31st May 2006

This leaflet has been produced using information from a number of sources. It is intended to be a summary of available information. For more detailed prescribing information please refer to the summary of product characteristics (www.medicines.org.uk).

Prepared by NHFT Medicines Management Committee September 2019
APPENDIX 2 - Advice to GPs for patients discharged on a combination of venlafaxine and mirtazapine

Theory for combination:

- Venlafaxine and its active metabolite inhibit synaptosomal reuptake of serotonin, noradrenaline and to a lesser extent dopamine to produce their antidepressant effect.
- Mirtazapine is a centrally active pre-synaptic alpha₂-antagonist, which increases central noradrenergic and serotonergic neurotransmission.

Noradrenaline neurotransmission is partly under the control of presynaptic alpha₂-adrenergic autoreceptors, which when stimulated by noradrenaline inhibit the release of noradrenaline into the synapse. There are other alpha₂-receptors (heteroreceptors) located on the presynaptic terminal end of serotonergic neurons which when stimulated by noradrenaline inhibit the release of serotonin. Blockade of these receptors would prevent this inhibition.

It is thought that mirtazapine enhances noradrenaline and serotonin transmission by blockade of these receptors thus the augmentation of venlafaxine with mirtazapine results in a synergistic effect on serotonergic systems.

Interactions:

Using combinations of serotonergic antidepressants increases the risk of developing serotonin syndrome. Where the patient is routinely prescribed any physical medicines that act on the serotonin system e.g. triptans, tramadol, St John’s Wort, a discussion should occur between the prescriber and the GP to ensure that these medicines are reviewed.

Serotonin syndrome is a potentially dangerous adverse reaction that is attributed to a toxic hyper-serotonergic state from hyper-stimulation of the brain stem and 5HT1A and 5HT2 receptors. Onset is usually within a few hours of drug or dose changes.

Symptoms of serotonin syndrome include and are usually a combination of at least three of the following:

- Mental state changes e.g. confusion, poor co-ordination, hypomania
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- Gastro intestinal side effects e.g. diarrhoea
- Hypertension
- Tachycardia
- Convulsions

Ensure all other causes have been ruled out e.g. infection, metabolic disturbances, substance misuse or withdrawal.
Monitoring:

The Summary of Product Characteristics of Efexor (venlafaxine) states that all patients should be carefully screened for high blood pressure and pre-existing hypertension should be controlled before initiation of treatment. It also recommends that blood pressure should be reviewed periodically, after initiation of treatment and after each dose increase of venlafaxine. Therefore it would be prudent to do the same with the combination.

However there are no guidelines available as to specific frequency of blood pressure monitoring nor is there guidance on specific actions to be taken if blood pressure increases. Locally a decision has been made that if there is an increase of greater than 10mm of mercury or BP reading is above 140 / 90 on two consecutive readings, advice should be sought from the consultant psychiatrist on treatment options. In all cases a risk/benefit discussion needs to take place with the patient, GP and Specialist to decide the safest option with regards to both mental and physical health.

Patient specific monitoring will be detailed in the accompanying clinic letter.

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