NICE Clinical guideline 23

Depression

Management of depression in primary and secondary care

Consultation on amendments to recommendations concerning venlafaxine

On 31 May 2006 the MHRA issued revised prescribing advice for venlafaxine (see http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2023843&ssTargetNodeId=389).

This document presents the proposed amendments to recommendations concerning venlafaxine in the NICE clinical guideline on depression. Comments are invited on the **proposed amended recommendations**. The **unchanged** recommendations are highlighted in grey and are not being consulted on.

1.5 Step 3: recognised depression in primary care – moderate or severe

Moderate or severe depression can be treated in both primary and secondary care and, as with mild depression, the choice of treatment will reflect patient preference, past experience of treatment and the fact that the patient may not have benefited from other interventions. With more severe depression, the risk of suicide should always be considered. Referral to secondary services should be based on this assessment, the degree of functional impairment and the presence of significant comorbidities or specific symptoms. Where trained mental health professionals are working in primary care, specialised treatments may be available in this setting.

1.5.1 Risk to self or others

1.5.1.1 Where a patient presents considerable immediate risk to self or others, urgent referral to a specialist mental health service should be arranged. **GPP**

1.5.2 Antidepressant drugs

There is more evidence for the effectiveness of antidepressant medication in moderate to severe depression than in milder depression. Antidepressants are as effective as psychological interventions, widely available and cost less. Careful monitoring of symptoms, side effects and suicide risk (particularly in those aged under 30) should be routinely undertaken, especially when initiating antidepressant medication. Patient preference and past experience of treatment, and particular patient characteristics should inform the choice of drug. It is also important to monitor patients for relapse and discontinuation/withdrawal symptoms when reducing or stopping medication. Patients should be warned about the risks of reducing or stopping medication.

Starting treatment

1.5.2.1 In moderate depression, antidepressant medication should be routinely offered to all patients before psychological interventions. **B**

1.5.2.2 Common concerns about taking medication should be addressed. For example, patients should be advised that craving and tolerance do not occur, and that taking medication should not be seen as a sign of weakness. **GPP**

1.5.2.3 All patients who are prescribed antidepressants should be informed, at the time that treatment is initiated, of potential side effects and of the risk of discontinuation/withdrawal symptoms. **C**

1.5.2.4 Patients started on antidepressants should be informed about the delay in onset of effect, the time course of treatment, the need to take medication as prescribed, and the possible discontinuation/withdrawal symptoms. Written information appropriate to the patient's needs should be made available. **GPP**

Monitoring risk

1.5.2.5 Patients started on antidepressants who are considered to present an increased suicide risk or are younger than 30 years (because of the potential increased risk of suicidal thoughts associated with the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered significant. **C**

1.5.2.6 For patients at high risk of suicide, a limited quantity of antidepressants should be prescribed. **C**

1.5.2.7 When a patient with depression is assessed to be at a high risk of suicide, the use of additional support such as more frequent direct contacts with primary care staff or telephone contacts should be considered. **C**

1.5.2.8 Particularly in the initial stages of SSRI treatment, healthcare professionals should actively seek out signs of akathisia, suicidal ideation, and increased anxiety and agitation. They should also advise patients of the risk of these symptoms in the early stages of treatment and advise them to seek help promptly if these are at all distressing. **C**

1.5.2.9 In the event that a patient develops marked and/or prolonged akathisia or agitation while taking an antidepressant, the use of the drug should be reviewed. **C**

Continuing treatment

1.5.2.10 Patients started on antidepressants who are not considered to be at increased risk of suicide should normally be seen after 2 weeks. Thereafter they should be seen on an appropriate and regular basis, for example, at intervals of 2–4 weeks in the first 3 months and at longer intervals thereafter, if response is good. **C**

1.5.2.11 Antidepressants should be continued for at least 6 months after remission of an episode of depression, because this greatly reduces the risk of relapse. **A**

1.5.2.12 When a patient has taken antidepressants for 6 months after remission, healthcare professionals should review with the patient the need for continued antidepressant treatment. This review should include consideration of the number of previous episodes, presence of residual symptoms, and concurrent psychosocial difficulties. **C**

The choice of antidepressants

1.5.2.13 When an antidepressant is to be prescribed in routine care, it should be a selective serotonin reuptake inhibitor (SSRI), because SSRIs are as effective as tricyclic antidepressants and are less likely to be discontinued because of side effects. **A**

1.5.2.14 When prescribing an SSRI, consideration should be given to using a product in a generic form. Fluoxetine and citalopram, for example, would be reasonable choices because they are generally associated with fewer discontinuation/withdrawal symptoms. However, fluoxetine is associated with a higher propensity for drug interactions. **C**

1.5.2.15 Dosulepin, phenelzine, combined antidepressants, and lithium augmentation of antidepressants should only be routinely initiated by specialist mental health professionals, including General Practitioners with a Special Interest in Mental Health. **C**

[Recommendations 1.5.2.16 and 1.5.2.17 in the original guidance deleted]

1.5.2.16 Toxicity in overdose should be considered when choosing an antidepressant for patients at significant risk of suicide. Healthcare professionals should be aware that the tricyclic antidepressants (with the exception of lofepramine) and venlafaxine are more dangerous in overdose than other equally effective drugs recommended for routine use in primary care.

1.5.2.17 If a depressed patient being treated with an SSRI develops increased agitation early in treatment, the prescriber should provide appropriate information, and if the patient prefers the drug should be changed to a different antidepressant. Alternatively, a brief period of concomitant treatment with a benzodiazepine should be considered, followed by a clinical review within 2 weeks. **C**

1.5.2.18 When a patient's depression fails to respond to the first antidepressant prescribed, the prescriber should check that the drug has been taken regularly and in the prescribed dose. **GPP**

1.5.2.19 If the response to a standard dose of an antidepressant is inadequate, and there are no significant side effects, a gradual increase in dose should be considered in line with the schedule suggested by the Summary of Product Characteristics. **C**

1.5.2.20 Prescribers should consider switching to another antidepressant if there has been no response at all after 1 month, but if there has been a partial response, a decision to switch can be postponed until 6 weeks. **C**

1.5.2.21 If an antidepressant has not been effective or is poorly tolerated and – after consideration of a range of other treatment options – the decision is made to offer a further course of antidepressants, then another single antidepressant should be prescribed. **C**

1.5.2.22 Reasonable choices for a second antidepressant include a different SSRI or mirtazapine, but consideration may also be given to other alternatives, including moclobemide,reboxetine and lofepramine. Other tricyclic antidepressants (except dosulepin) and venlafaxine may be considered, especially for severe depression where assessment does not identify significant risk of suicide. **B**

1.5.2.23 When switching from one antidepressant to another, prescribers should be aware of the need for gradual and modest incremental increases of dose, of interactions between antidepressants and the risk of serotonin syndrome when combinations of serotonergic antidepressants are prescribed. Features include confusion, delirium, shivering, sweating, changes in blood pressure and myoclonus. **C**

1.5.2.24 Before prescribing mirtazapine, practitioners should take into account its propensity to cause sedation and weight gain. **A**

1.5.2.25 Before prescribing moclobemide, practitioners should take into account the need to wash out previously prescribed antidepressants. **A**

1.5.2.26 Before prescribing reboxetine, practitioners should take into account the relative lack of data on side effects. Patients taking reboxetine should be monitored carefully. **B**

1.5.2.27 Before prescribing tricyclic antidepressants, practitioners should take into account their poorer tolerability compared with other equally effective

antidepressants, the increased risk of cardiotoxicity and their toxicity in overdose. **B**

1.5.2.28 Where a tricyclic is chosen as an antidepressant, lofepramine is a reasonable choice because of its relative lack of cardiotoxicity. **C**

1.5.2.29 Patients who start on low-dose tricyclic antidepressants and who have a clear clinical response may be maintained on that dose with careful monitoring. **C**

1.5.2.30 Patients started on low-dose tricyclic antidepressants should be carefully monitored for side effects and efficacy, and the dose gradually increased if there is lack of efficacy and no major side effects. **GPP**

1.5.2.31 Before prescribing venlafaxine, practitioners should take into account the increased likelihood of patients stopping treatment because of side effects, compared with equally effective SSRIs.

1.5.2.32 Before prescribing venlafaxine, practitioners should take into account its higher propensity for discontinuation/withdrawal symptoms if stopped abruptly, its toxicity in overdose and its higher cost.

1.5.2.33 Before prescribing venlafaxine, ensure pre-existing hypertension is controlled in line with current NICE guidelines. Venlafaxine should not be prescribed for patients with uncontrolled hypertension.

1.5.2.34 For patients prescribed venlafaxine, blood pressure should be checked on initiation, and regularly during treatment particularly during dosage titration. Reduce the dose or consider discontinuation in patients experiencing a sustained increase in blood pressure.

1.5.2.35 For patients prescribed venlafaxine, consideration should be given to monitoring of cardiac function particularly in those with known cardiovascular disease or risk factors for cardiovascular disease

1.5.2.36 When prescribing venlafaxine be aware of clinically significant interactions with concomitant drugs, for example, serotonergic drugs, antifungal drugs, and HIV protease inhibitors.

1.5.2.37 Venlafaxine should only be prescribed at high dose (300 mg/day or more) under the supervision or advice of a specialist mental health medical practitioner.

1.5.2.38 Although there is evidence that St John's wort may be of benefit in mild or moderate depression, healthcare professionals should not prescribe or advise its use by patients because of uncertainty about appropriate doses, variation in the nature of preparations and potential serious interactions with other drugs (including oral contraceptives, anticoagulants and anticonvulsants). **C**

1.5.2.39 Patients who are taking St John's wort should be informed of the different potencies of the preparations available and the uncertainty that arises from this. They should also be informed of the potential serious interactions of St John's wort with other drugs (including oral contraceptives, anticoagulants and anticonvulsants). **C**

Patient characteristics

Gender

1.5.2.40 When considering which antidepressants to prescribe for female patients, the fact that they have poorer tolerance of imipramine should be taken into account. **B**

Age

1.5.2.41 For older adults with depression, antidepressant treatment should be given at an age-appropriate dose for a minimum of 6 weeks before treatment is considered to be ineffective. If there has been a partial response within this period, treatment should be continued for a further 6 weeks. **C**

1.5.2.42 When prescribing antidepressants – in particular tricyclics – for older adults with depression, careful monitoring for side effects should be undertaken. **C**

1.5.2.43 Healthcare professionals should be aware of the increased frequency of drug interactions when prescribing an antidepressant to older adults who are taking other medications. **GPP**

Patients with dementia

1.5.2.44 Depression in patients with dementia should be treated in the same way as depression in other older adults. **C**

1.5.2.45 Healthcare professionals should be aware that depression responds to antidepressants even in the presence of dementia. **C**

Patients with cardiovascular disease

1.5.2.46 When initiating treatment in a patient with a recent myocardial infarction or unstable angina, sertraline is the treatment of choice as it has the most evidence for safe use in this situation. **B**

1.5.2.47 Healthcare professionals should take account of the increased risks associated with tricyclic antidepressants in patients with cardiovascular disease. **GPP**

1.5.2.48 An ECG should be carried out and blood pressure measurement taken before prescribing a tricyclic antidepressant for a depressed patient at significant risk of cardiovascular disease. **GPP**

1.5.2.49 Venlafaxine should not be prescribed for patients with:

- High risk of cardiac arrhythymias
- A recent myocardial infarction
- Uncontrolled hypertension.

Stopping or reducing antidepressants

Although antidepressants are not associated with tolerance and craving, as experienced when withdrawing from addictive substances such as opiates or alcohol, some patients experience symptoms when stopping antidepressants or reducing the dose. These can include dizziness, nausea, paraesthesia, anxiety and headaches and, in this guideline, are referred to as discontinuation/withdrawal symptoms.

1.5.2.50 All patients prescribed antidepressants should be informed that, although the drugs are not associated with tolerance and craving, discontinuation/withdrawal symptoms may occur on stopping, missing doses or, occasionally, on reducing the dose of the drug. These symptoms are usually mild and self-limiting but can occasionally be severe, particularly if the drug is stopped abruptly. **C**

1.5.2.51 Patients should be advised to take the drugs as prescribed. This may be particularly important for drugs with a shorter half-life, such as paroxetine, in order to avoid discontinuation/withdrawal symptoms. **C**

1.5.2.52 Healthcare professionals should normally gradually reduce the doses of the drug over a 4-week period, although some people may require longer periods. Fluoxetine can usually be stopped over a shorter period. **C**

1.5.2.53 If discontinuation/withdrawal symptoms are mild, practitioners should reassure the patient and monitor symptoms. If symptoms are severe, the practitioner should consider reintroducing the original antidepressant at the dose that was effective (or another antidepressant with a longer half-life from the same class) and reduce gradually while monitoring symptoms. **C**

1.5.2.54 Healthcare professionals should inform patients that they should seek advice from their medical practitioner if they experience significant discontinuation/withdrawal symptoms. **GPP**

1.5.3 Psychological treatments

For moderate to severe depression, a number of structured psychological interventions of longer duration (usually of 16 to 20 sessions) from an appropriately trained member of the mental health team are effective. In addition to the evidence for their effectiveness, the choice of treatment will reflect patient preference and past experience of treatment. Most patients receiving these interventions will not have benefited from other interventions. The same principles underpinning the use of psychological therapies outlined for the treatment of mild depression (Step 2) also apply here.

Where depression is comorbid with another significant disorder, such as personality disorder, then treatment may need to be extended or varied.

Cognitive behavioural therapies and interpersonal therapy

The following recommendations focus on the provision of CBT. However, IPT can also be an effective treatment for depression. Where patient preference or clinician opinion favours the use of IPT, it may be appropriate to draw the patient's attention to the more limited evidence base for this therapy.

1.5.3.1 When considering individual psychological treatments for moderate, severe and treatment-resistant depression, the treatment of choice is CBT. IPT should be considered if the patient expresses a preference for it or if, in the view of the healthcare professional, the patient may benefit from it. **B**

1.5.3.2 For moderate and severe depression, the duration of all psychological treatments should typically be in the range of 16 to 20 sessions over 6 to 9 months. **B**

1.5.3.3 CBT should be offered to patients with moderate or severe depression who do not take or who refuse antidepressant treatment. **B**

1.5.3.4 CBT should be considered for patients who have not had an adequate response to a range of other treatments for depression (for example, antidepressants and brief psychological interventions). **C**

1.5.3.5 CBT should be considered for patients with severe depression in whom the avoidance of side effects often associated with antidepressants is a clinical priority or personal preference. **B**

1.5.3.6 For patients with severe depression who are starting a course of CBT, consideration should be given to providing 2 sessions per week for the first month of treatment. **C**

1.5.3.7 Where patients have responded to a course of individual CBT, consideration should be given to follow-up sessions, which typically consist of 2 to 4 sessions over 12 months. **C**

Initial presentation of severe depression

1.5.3.8 When patients present initially with severe depression, a combination of antidepressants and individual CBT should be considered as the combination is more cost-effective than either treatment on its own. **B**

Couple-focused therapy

1.5.3.9 Couple-focused therapy should be considered for patients with depression who have a regular partner and who have not benefited from a brief individual intervention. An adequate course of couple-focused therapy should be 15 to 20 sessions over 5 to 6 months. **B**

Psychodynamic psychotherapy

1.5.3.10 Psychodynamic psychotherapy may be considered for the treatment of the complex comorbidities that may be present along with depression. **C**

1.5.4 Atypical depression

Depression can present with atypical features, commonly over-eating and over-sleeping. The syndrome is also associated with mood reactivity and a longstanding pattern of interpersonal rejection and over-sensitivity. In comparison with major depressive disorder without atypical features, patients with atypical features are more often female, have a younger age of onset and a more severe degree of

psychomotor slowing. Coexisting diagnoses of panic disorder, substance abuse and somatisation disorder are also common.

1.5.4.1 Patients whose depression has atypical features should be treated with an SSRI. **C**

1.5.4.2 Referral to mental health specialists should be considered for patients with atypical depression and significant functional impairment who have not responded to an SSRI. **GPP**

1.5.5 Chronic depression

Chronic depression is diagnosed when a person meets the diagnostic criteria for depression for at least 2 years. Such patients may require combination treatments and attention to social and support factors that may maintain or ameliorate their difficulties. Patients who have had chronic depression may require rehabilitation to help them regain confidence to return to more independent living. People who have had severe or chronic depression may require special help in returning to work. Work provides a number of protective factors for depression including structure to a day, social contacts and self-esteem.

1.5.5.1 Patients with chronic depression should be offered a combination of CBT and antidepressant medication. **A**

1.5.5.2 For male patients with chronic depression who have not responded to an SSRI, consideration should be given to a tricyclic antidepressant because men tolerate the side effects of tricyclic antidepressants reasonably well. **C**

1.5.5.3 For people with chronic depression who would benefit from additional social support, befriending should be considered as an adjunct to pharmacological or psychological treatments. Befriending should be by trained volunteers providing, typically, at least weekly contact for between 2 and 6 months. **C**

1.5.5.4 Where a patient's depression has resulted in loss of work or disengagement from other social activities over a longer term, a

rehabilitation programme addressing these difficulties should be considered. **C**

1.5.6 Enhanced care in primary care

In primary care, the following strategies can improve the effectiveness of treatments offered.

1.5.6.1 The provision of telephone support by appropriately trained members of the primary care team, informed by clear treatment protocols, should be considered for all patients, in particular for the monitoring of antidepressant medication regimes. **B**

1.5.6.2 Primary care organisations should consider establishing multifaceted care programmes that integrate – through clearly specified protocols – the delivery and monitoring of appropriate psychological and pharmacological interventions for the care of people with depression. **C**

1.6 Step 4: specialist mental health services – treatment-resistant, recurrent, atypical and psychotic depression, and those at significant risk

Specialist mental health professionals, including GPs with a Special Interest in mental health, provide assessment, treatment and consultancy services for this group of patients. They may do this in secondary care services or through attachment to primary care mental health teams. Patients may enter care directly at this step if they are assessed as requiring specialist services.

1.6.1.1 The assessment of patients with depression referred to specialist mental health services should include a full assessment of their symptom profile and suicide risk and, where appropriate, previous treatment history. Assessment of psychosocial stressors, personality factors and significant relationship difficulties should also be undertaken, particularly where the depression is chronic or recurrent. **GPP**

1.6.1.2 In specialist mental health services, after a thorough review of previous treatments for depression has been undertaken, consideration should be given to re-introducing previous treatments that have been inadequately delivered or adhered to. **GPP**

1.6.1.3 Crisis resolution and home treatment teams should be used as a means of managing crises for patients with severe depression who are assessed as presenting significant risk, and as a means of delivering high-quality acute care. In this context, teams should pay particular attention to risk monitoring as a high-priority routine activity in a way that allows people to continue their normal lives without disruption. **C**

1.6.1.4 Medication in secondary-care mental health services should be initiated under the supervision of a consultant psychiatrist. **GPP**

1.6.2 Treatment-resistant depression

Some people with depression do not respond well to initial treatment. This guideline defines treatment-resistant depression as that which fails to respond to two or more antidepressants given sequentially at an adequate dose for an adequate time. Patients whose depression is treatment-resistant may benefit from psychological interventions. For chronically depressed patients, the combination of pharmacological and psychological treatment may be particularly effective. Patient preference, the level of risk, social and personal circumstances, and the drawbacks of all interventions will influence the choice of treatment.

Combined psychological and drug treatment

1.6.2.1 For patients whose depression is treatment-resistant, the combination of antidepressant medication with CBT should be considered. **B**

1.6.2.2 For patients with treatment-resistant moderate depression who have relapsed while taking, or after finishing, a course of antidepressants, the combination of antidepressant medication with CBT should be considered. **B**

Drug treatments

1.6.2.3 A trial of lithium augmentation should be considered for patients whose depression has failed to respond to several antidepressants and who are prepared to tolerate the burdens associated with its use. **B**

1.6.2.4 Before initiating lithium augmentation, an ECG should be carried out. **C**

1.6.2.5 Venlafaxine should be considered for patients whose depression has failed to respond to two adequate trials of other antidepressants. Consideration should be given to increasing the dose up to *BNF* limits if required, provided patients can tolerate the side effects. **C**

[Venlafaxine recommendations (1.6.2.6 to 1.6.2.9 in the original) deleted from this section]

1.6.2.6 Augmenting an antidepressant with another antidepressant should be considered for patients whose depression is treatment resistant and who are prepared to tolerate the side effects. There is evidence for benefits from the addition of mianserin or mirtazapine to SSRIs. **C**

1.6.2.7 Where patients are treated with one antidepressant augmented by another, careful monitoring of progress and side effects is advised and the importance of this should be explained to the patient. Particular care should be taken to monitor for serotonin syndrome. **GPP**

1.6.2.8 When used to augment another antidepressant, mianserin should be used with caution, particularly in older adults, because of the risk of agranulocytosis. **C**

1.6.2.9 Where combinations of antidepressants other than mianserin with SSRIs and mirtazapine with SSRIs are considered, healthcare professionals should re-evaluate the adequacy of previous treatments carefully before proceeding, and consider seeking a second opinion. Any discussion should be documented in the notes. **C**

1.6.2.10 Phenelzine should be considered for patients whose depression has failed to respond to alternative antidepressants and who are prepared to tolerate

the side effects and dietary restrictions associated with its use. However, its toxicity in overdose should be considered when prescribing for patients at high risk of suicide. **C**

1.6.2.11 Augmentation of an antidepressant with carbamazepine, lamotrigrine, buspirone, pindolol, valproate or thyroid supplementation is not recommended in the routine management of treatment-resistant depression. **B**

1.6.2.12 Dosulepin should not be initiated routinely because evidence supporting its tolerability relative to other antidepressants is outweighed by the increased cardiac risk and toxicity in overdose. **C**

1.6.2.13 There is insufficient evidence to recommend the use of benzodiazepine augmentation of antidepressants. **C**

Referral

1.6.2.14 When a patient's depression has failed to respond to various strategies for augmentation and combination treatments, referral to a clinician with a specialist interest in treating depression should be considered. **GPP**