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Please note that this current guideline is currently being updated in line with Lincolnshire Partnership Foundation Trust's guidance. In the interim, should you require any additional guidance or information, please refer to: https://cks.nice.org.uk/depression. Alternatively, please contact the LPFT pharmacy team for further advice via: lpn-tr.pharmacy@nhs.net

CLINICAL GUIDELINES FOR ANTIDEPRESSANT USE IN PRIMARY AND SECONDARY CARE

Lincolnshire Partnership Foundation Trust in conjunction with Lincolnshire PACEF have recently updated and expanded local guidance on the use of antidepressant drugs for the treatment of depression. This revision was necessitated by the publication of NICE Clinical Guidelines 90 and 91: *Depression - Treatment and management of depression in adults, including adults with a chronic physical health problem* (October 2009). It is the purpose of this special edition of the *PACE Bulletin* to summarize the key points of local guidance and the NICE Clinical Guidelines with particular relevance to the management of depression in primary care. The full text LPFT document can be accessed in the PACEF section of www.lincolnshire.nhs.uk

Treatment of Mild Depression in Primary Care

- **Antidepressant medication is not recommended for the initial treatment of mild symptoms of depression.** The risks of antidepressant drugs are well documented and the benefits in mild depression unsubstantiated; randomised controlled trial evidence indicates little difference in outcome between antidepressant medication and placebo.
- Antidepressants should be considered for patients with mild depression that persists after other interventions have failed, in those whose depression is associated with psychosocial and medical problems and when those with a past history of moderate or severe depression present with mild depression.
- Many patients with mild depression respond to interventions such as exercise or guided self-help; many improve while being monitored without any additional help (so-called 'active monitoring'). More structured therapies, such as problem-solving, brief cognitive behavioural therapy (CBT) or counselling can be helpful.

Treatment of Moderate or Severe Depression in Primary Care

Antidepressant treatment should be considered for people with:

- Sub-threshold depressive symptoms present for at least 2 years.
- Sub-threshold depressive symptoms or mild depression persisting after other interventions.
- Mild depression that complicates the care of a chronic physical health problem.
- Moderate depression.
- A chronic physical health problem and presenting with moderate depression, after other interventions have been attempted or rejected by the person.
- A past history of severe depression or presenting with severe depression.

Antidepressant Selection: First Line

- **There is more evidence for the effectiveness of antidepressant medication in the treatment of moderate to severe depression.** Antidepressants have been shown to be as effective as psychological interventions, are widely available and cost less.
- In the primary care setting, there appears to be little difference in terms of efficacy between different antidepressant drugs; there are, however, differences in terms of side effect profile, potential for interactions and safety in overdose which will necessitate some degree of tailoring of therapy to the individual patient.
- **NICE Clinical Guidelines 90 and 91 advocate fluoxetine, citalopram or sertraline as preferred first line antidepressant choices.** SSRIs are favoured first line because they are as effective as other antidepressants, better tolerated than many, less cardiotoxic, safer in overdose and generally less expensive (with the exception of escitalopram). Dose titration is not routinely required, so inadvertent prescribing of sub-therapeutic doses is less likely to occur.
- **In co-morbid depression with anxiety, generic citalopram is the preferred alternative. Citalopram and fluoxetine are also preferred in patients at risk of self-harm. Citalopram should be used with caution (and preferably avoided) in patients with established cardiac disease that may increase the risk of ventricular arrhythmias (e.g. recent MI).**
- **Of the generic SSRIs, sertraline has evidence of superior tolerability and is also the preferred agent in people with ischaemic heart disease (e.g. post MI, unstable angina).**
- **People receiving antidepressant treatment for a first episode presentation should be advised to continue medication for a minimum of 6 months after remission or for 2 years or more in those at a risk of relapse.**
- **People who have had two or more depressive episodes in the recent past and who have experienced significant functional impairment during the episodes should be advised to continue treatment for at least 2 years.**
- **Under no circumstances should a sub-therapeutic dose of an antidepressant be used to treat depression**: a diagnosis of mild depression does not necessitate pharmacological intervention in most instances; in moderate to severe depression a full course of an appropriate agent, prescribed at a treatment dose is indicated.
- The Medicines and Healthcare products Regulatory Agency (MHRA) / Committee on Safety of Medicines (CSM) Expert Working Group on SSRIs recommended that **SSRIs should be prescribed at the lowest possible therapeutic dose** (fluoxetine 20mg once daily; citalopram 20mg once daily). Patients should be monitored closely in the early stages of treatment for restlessness, agitation and suicidality (particularly if the patient is below 30). Doses should be tapered gradually on stopping.
- Patients should be given appropriate information on the nature, course and treatment of depression, including the use and likely side effects of medication (particularly akathesia, increased anxiety, increased agitation), the possibility of discontinuation/withdrawal symptoms and potential interactions with concomitant medicines or physical illness. Patients should be advised of the time lag for antidepressants to start working effectively.
- Patients should be reminded of the importance of taking the treatment as prescribed. Poor patient concordance is a significant contributor to treatment failure. Compliance rates of between 40% and 90% (mean 65%) have been recorded in different studies. It is recommended that all patients initiated on an antidepressant should be reviewed after the first 2-4 weeks of treatment in order to assess tolerance and concordance.
- The initial antidepressant should be monitored for response over 3-4 weeks. If no response is seen, increasing dose or switching antidepressant should be considered. If a partial response is seen, continue treatment for a further 2-4 weeks and re-assess. When switching of antidepressants becomes necessary, refer to the table on Appendix 1 for guidance.

- **Do not prescribe or advise the use of St John's Wort for depression.** Different preparations tend to vary in potency and there is significant potential for serious interactions with other drugs including oral contraceptives, anticoagulants and anticonvulsants.

Antidepressant Selection: Second Line

- **Potential second line agents include: other SSRIs (such as escitalopram), TCAs (particularly lofepramine), mirtazepine, venlafaxine (below 300mg), trazodone and moclobemide.**
- **Escitalopram is the s-enantiomer of citalopram. It is at least as effective as other SSRIs and marginally better tolerated (except for sertraline). The evidence for the clinical superiority of escitalopram is limited to the treatment of severe depression; any clinical advantage must be balanced against the higher cost of escitalopram when compared to alternative generic SSRIs. Escitalopram may be considered second line for people with severe depression who have shown an antidepressant response to other SSRIs but have been unable to tolerate side-effects. It should not be used first line or to treat people who have failed to respond to other SSRIs.**
- **Mirtazapine is a potentially useful second line agent when first-line SSRIs have failed to induce an adequate response or are poorly tolerated.** It is also useful in the augmentation of other antidepressants in treatment-resistant depression (although trial evidence is limited). Other potential roles are in patients with depression with co-existing anxiety or sleep disturbance and those with prostatism, glaucoma, poorly controlled epilepsy, or diabetes.
- **Lofepramine remains the best tolerated and safest tricyclic antidepressant and should be prescribed as the tricyclic of choice where a tricyclic is indicated (e.g. when sedation is required).**
- **NICE recommend that people should not be switched to, or started on, dosulepin because evidence supporting its tolerability relative to other antidepressants is outweighed by the increased cardiac risk and toxicity in overdose.**
- **Amitriptyline should not be initiated routinely in depression because of similar concerns over increased cardiac risk and toxicity in overdose.**
- The degree of sedation associated with TCAs varies from agent to agent, with imipramine, lofepramine and nortriptyline being less sedative than other options.
- **Earlier restrictions on venlafaxine use have been partially reversed. Current evidence suggests that venlafaxine is probably not cardiotoxic. However, it is associated with a greater risk of death in overdose than other equally effective antidepressants recommended in primary care.**
- **Venlafaxine, moclobemide and lofepramine should be used with caution (and preferably avoided) in patients with established cardiac disease that may increase the risk of ventricular arrhythmias (e.g. recent MI).**

Antidepressant Selection: Third Line

- **Third line agents that should only be initiated by a mental health specialist include: paroxetine, fluvoxamine, reboxetine, duloxetine, phenelzine, isocarboxazid, tranylcypramine, mianserin, agomelatine, flupenthixol, tryptophan, venlafaxine (above 300mg) and lithium.**
- High dose venlafaxine remains contraindicated in patients with an identified very high risk of serious cardiac ventricular arrhythmia (e.g. those with a significant left ventricular dysfunction (NYHA Class III/IV)) and in patients with uncontrolled hypertension. Venlafaxine is no longer contra-indicated in patients with electrolyte imbalance.

- Duloxetine (Cymbalta) is promoted as an alternative Selective Serotonin and Noradrenaline Reuptake Inhibitor (SNRI) to venlafaxine without QTc complex prolongation, or need for BP monitoring in patients without pre-existing hypertension. However, due to the lack of long-term efficacy and safety data, PACEF strongly recommend initiation by specialists only. Prescribers are reminded that duloxetine is a black triangle drug and that all suspected adverse drug reactions must be reported via the MHRA Yellow Card scheme. Duloxetine (Cymbalta) is designated AMBER.
- Paroxetine is associated with a higher incidence of sweating, sedation and sexual dysfunction than other SSRIs and with significantly more problems on discontinuation. It has a number of potential drug-drug interactions, due to its effect on hepatic enzymes. It should not be used in patients taking atomoxetine. Paroxetine retains a role in the treatment of some anxiety disorders.
- Fluvoxamine is associated with a higher incidence of nausea than other SSRIs. It interacts significantly with a number of other drugs including clozapine, due to an effect on hepatic enzymes. It is not widely prescribed. Fluvoxamine should be avoided in patients taking theophylline, clozapine, methadone or tizanidine.
- Reboxetine is a relatively selective noradrenaline reuptake inhibitor (NARI). It is not licensed for use in older adults. The Cipriani meta-analysis of head-to-head trials of antidepressants was unfavourable to reboxetine in terms of both response rate and tolerability.

Summary of PACEF Decisions: Antidepressants

Drug	Indication(s)	Traffic Light Status
First line		
Citalopram tablets (generic)	**Depressive illness in the initial phase and as maintenance therapy against potential relapse or recurrence.**	**GREEN** **First line option**
Fluoxetine capsules (generic)	**Major depression**	**GREEN** **First line option**
Sertraline tablets (generic)	**Depression**	**GREEN** **First line option**
Second Line		
Clomipramine capsules (generic)	Depressive illness	GREEN Second line option
Escitalopram tablets (Cipralex)	Depression	GREEN Second line option
Imipramine tablets (generic)	Depressive illness	GREEN Second line option
Lofepramine tablets (generic)	Depressive illness	GREEN Second line option; preferred TCA.
Mirtazepine tablets (generic)	Depressive illness	GREEN Second line option
Moclobemide tablets (generic)	Major depression	GREEN Second line option; preferably avoid in those with established cardiac disease.
Nortriptyline tablets (Allegron)	Depressive illness	GREEN Second line option Other indications are approved (e.g. neuropathic pain).
Trazodone capsules/tablets (generic)	Depressive illness, particularly where sedation is required	GREEN Second line option
Venlafaxine tablets (Efexor)/ modified release capsules (Efexor XL)	Major depressive disorder; prevention of relapse or recurrence of depression, depression with anxiety.	GREEN Second line option; preferably avoid in those with established cardiac disease.
Third Line		
Agomelatine tablets (Valdoxan)	Major depression	RED

		For use within LPFT only
Amitriptyline tablets	Depressive illness	AMBER for depression Not recommended for the routine treatment of depression due to high rate of fatality in overdose. Other indications are approved (e.g. neuropathic pain).
Duloxetine capsules (Cymbalta)	Depression	AMBER Third line option
Fluvoxamine tablets	Depressive illness	AMBER Third line option
Isocarboxazid tablest	Depressive illness	AMBER Third line option
Mianserin tablets	Depressive illness, particularly where sedation is required	AMBER Third line option
Paroxetine tablets	Major depression	AMBER Third line option
Phenelzine tablets (Nardil)	Depressive illness	AMBER Third line option
Reboxetine tablets (Edronax)	Major depression	AMBER Third line option
Tranylcypromine tablets	Depressive illness	AMBER Third line option
Tryptophan tablets (Optimax)	An adjunctive therapy for depression resistant to standard antidepressants.	AMBER Third line option as an adjunct
Venlafaxine tablets (Efexor)	Severely depressed or hospitalized patients who require doses of 300mg daily or above.	AMBER Should only be initiated under specialist supervision
Venlafaxine tablets (Efexor)/ modified release capsules (Efexor XL)	Depression necessitating concurrent SSRI and venlafaxine treatment	AMBER Should only be initiated under specialist supervision
Not Recommended		
Dosulepin capsules/tablets (generic/all brands)	Depression; anxiety associated with depression	RED-RED Not recommended for the treatment of depression due to high rate of fatality in overdose.
St Johns Wort preparations	Depression	RED-RED St John's Wort preparations should not be prescribed or recommended for purchase due to variation in potency between different preparations and the serious risk of interaction with other medication.

Appendix 1
Guidance on the switching of antidepressants

The following table includes switches likely to be prescribed in general practice.

To: / From:	TCA	Citalopram Escitalopram Sertraline	Fluoxetine	Trazodone	Moclobemide	Venlafaxine	Duloxetine	Mirtazapine
TCA	**CT**	**CT**	**CT**	**CT**	**7d**	**CT** starting at 37.5mg	**CT**	**CT**
Citalopram Escitalopram Sertraline	**CT**	**CT** Withdraw drug 1 and start drug 2 at half usual dose	**CT** Withdraw drug 1 and start drug 2 at half usual dose	**Stop SSRI first**	**7d** (14d if sertraline)	**CT** Start venlafaxine at 37.5mg, increase slowly	**CT** or Stop SSRI and start duloxetine 60mg daily	**CT**
Fluoxetine	**4-7d**	**4-7d**		**4-7d**	**5 week** washout	**W** Start venlafaxine	**CT** or Stop SSRI and start	**4-7d**

						at 37.5mg, increase slowly	dulox etine 60mg daily	
Trazodone	**CT**	**W**	**W**		**7d**	**CT** Start venlafax ine at 37.5mg	**CT**	**W**
Moclobemide	**1d**	**1d**	**1d**	**1d**		**1d**	**1d**	**1d**
Venlafax ine	**CT**	**CT** Withdraw drug 1 and start drug 2 at half usual dose	**CT** Withdraw drug 1 and start drug 2 at half usual dose	**CT**	**7d**		**W**	**CT**
Dulox etine	**CT**	**1d**	**1d**	**1d**	**7d**	**1d**		**1d**
Mirtazapine	**W**	**W**	**W**	**W**	**7d**	**CT**	**W**	

Key
CT: Careful cross-taper, start drug 2 at a low dose
W: Withdraw drug 1 before starting drug 2, no w ashout period required
#d: Allow for a w ashout period of # days after stopping drug 1 before starting drug 2 at a low dose.

References

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Cipriani A et al., Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis, *Lancet* 2009; 373:746-58
Lincolnshire Partnership NHS Foundation Trust, *Guidance relating to the use of Antidepressant Medicines in Primary and Secondary Care* (February 2010).
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