

Prescribing guidelines for treatment of Depression in Adults and Older Adults

Basic principles

- Antidepressants are suitable for the treatment of moderate to severe depression
- A diagnosis of Bipolar Affective Disorder should be excluded before they are prescribed.
- Treatment should continue for 6-9 months after remission from a single episode¹.
- Patients with two prior episodes of depression or with additional relapse risk factors should be treated for two years or longer².
- There is a 50% chance of relapse if antidepressants are discontinued immediately after recovery
- Risk of relapse increases with each episode of depression.
- Clinical trials show antidepressants to be effective in ~ 50% of patients with moderate depression², although naturalistic studies suggest that several changes in treatment may be needed before remission is achieved – STAR*D¹
- Although it is commonly advised that antidepressants may take four weeks to work, studies have recently shown that their onset of action may be much quicker (1-2 weeks)³.
- If no effect is seen within two weeks it is important to monitor the patient more closely and consider changing the dose or drug at weeks 3-4.
- Maintenance treatment doses should be the same or close to the acute treatment dose.
- Withdraw antidepressants gradually to avoid discontinuation symptoms.
- Risk of relapse is highest in the first 2-3 months after withdrawal, regardless of the previous length of treatment.
- Consider the suicide risk and choose a drug with a low toxicity risk if possible (see below)
- Monitor efficacy of treatment plan regularly – offer telephone support where necessary

Choice of treatment:

Choice of antidepressant should be based on the personal preference of the patient taking into account the relative adverse effects of various antidepressants, pre-existing medical conditions, self harm risks and potential interactions with other medication.

Also consider any co-morbid psychiatric disorder that may require a particular class of antidepressant e.g. OCD (SSRI/Clomipramine), anxiety disorders (SSRI), bipolar illness (SSRIs less likely to cause manic switch than TCAs/MAOIs)

Pregnancy and Lactation

Tricyclics are the drugs of choice in pregnancy. These should be considered in women of child-bearing age who plan to become pregnant in the near future. Sertraline, imipramine and nortriptyline are the drugs of choice in lactation. For further advice see our MI bulletin **Antidepressants in Pregnancy and Lactation June 2010 (link)**

Special Populations

Brief advice is given below about the first choice (lower risk) medicines that can be used in these populations. Other anti-depressants may also be suitable, depending on the individual. If you need further advice, contact Oxford Health Medicines Information. Med.Info@oxfordhealth.nhs.uk Tel: 01865 455716.

Elderly – SSRIs or mirtazapine; Watch for hyponatraemia ([FAQ link](#)), co-morbid illness and interactions with other medication. Gastro protection may be advised where concomitant administration of SSRIs with NSAIDs

Epilepsy – SSRIs; citalopram is less likely to interact with anticonvulsants. Also may need to review anticonvulsants as some have been reported to cause depression. ([FAQ link](#))

Hepatic impairment – Paroxetine or agomelatine*. Use lower doses and monitor for adverse effects regularly. Watch out for hepatic drug interactions.

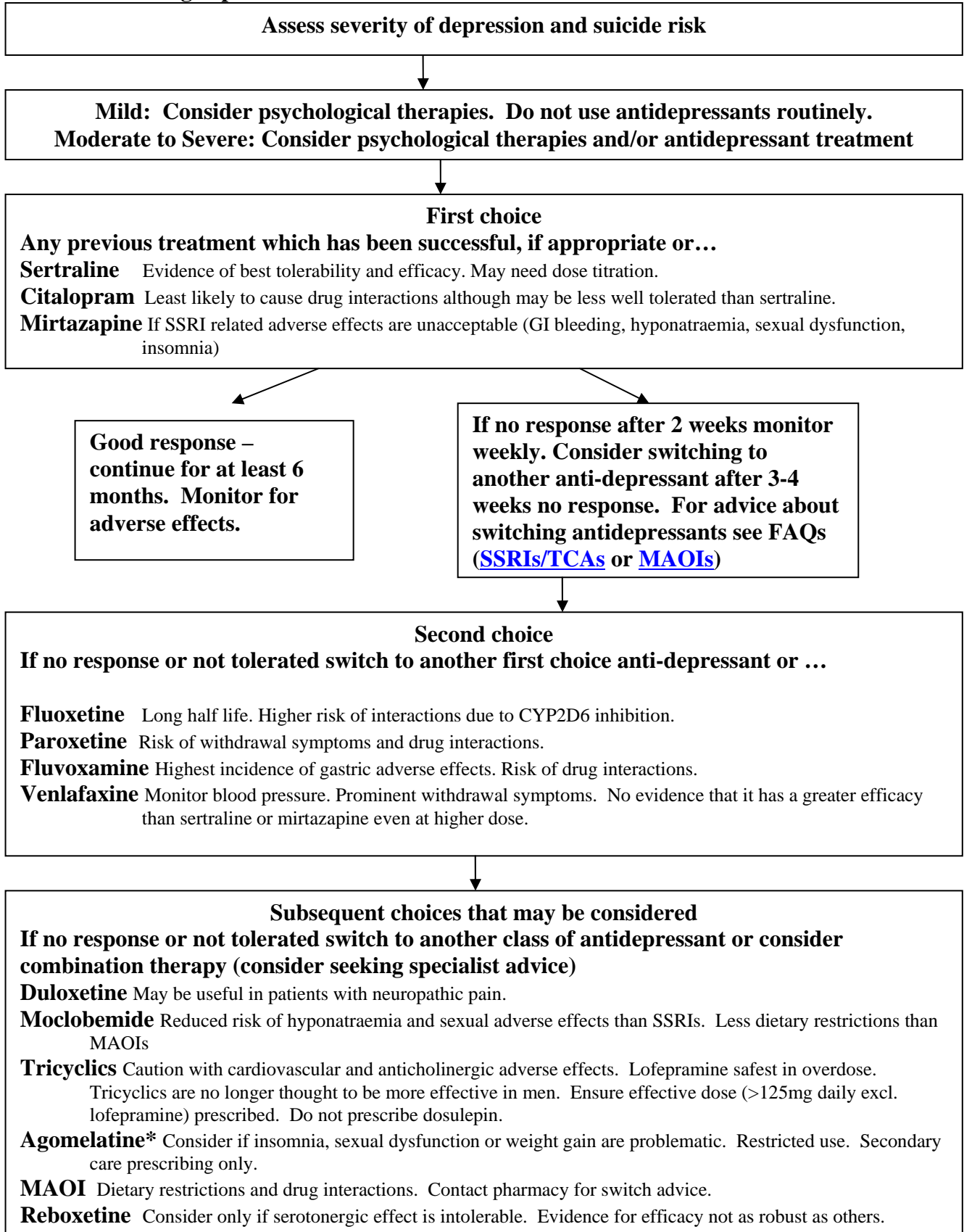
Renal impairment – SSRIs; choose one with short half life (sertraline, paroxetine) unless concerned about drug interactions (citalopram). Moclobemide, agomelatine* and tricyclics are also lower risk, although monitor for urinary retention³.

Cardiovascular disease SSRIs (sertraline), mirtazapine. ([FAQ link](#)) Avoid tricyclics and venlafaxine if possible.

Parkinsons – SSRIs; monitor for movement disorders. Depression is often difficult to treat. ([FAQ link](#))

Diabetes – Sertraline is the drug of choice³. SSRIs may decrease weight and glucose in the short term, but long term moderate / high dose antidepressant use may be associated with an increased incidence of diabetes^{1,3}.

Flowchart for treating depression :



*Agomelatine is not currently prescribed by GPs in Oxfordshire and Buckinghamshire (see below)

Non-generic antidepressants: - (please also refer to PCT traffic lighting for individual drugs)

Escitalopram is the active enantiomer of citalopram. In a recent meta-analysis based on 117 clinical trials comparing 12 antidepressants, escitalopram was in the top four antidepressants for both tolerability and effectiveness⁴. NICE used this study data in their economic evaluation of antidepressants in 2010 and found mirtazapine to be the most cost-effective antidepressant for moderate to severe depression, with sertraline being second and escitalopram third. In their final recommendations they say to 'normally choose an SSRI in generic form' as first choice². Escitalopram is currently not recommended for prescribing for depression within Oxford Health NHS FT or within Oxfordshire or Bucks PCTs.

Duloxetine is an SNRI licensed for depression. Within the meta-analysis mentioned above it fared badly, although the manufacturers argue that the authors omitted several relevant duloxetine studies. It received its licence in 2008. At that time it was felt that antidepressants which had dual serotonergic and noradrenergic (e.g. venlafaxine) might be more effective in treatment resistant depression. Recent evidence doesn't support this theory⁴. Duloxetine is also licensed for the treatment of diabetic neuropathy, generalised anxiety disorder (Cymbalta[®]) and stress urinary incontinence (Yentreve[®]).

Agomelatine, a new antidepressant, has two main areas of activity; stimulation of melatonin MT₁ and MT₂ receptors which enhances sleep and inhibition of post-synaptic serotonin 5HT_{2C} receptors (similar to mirtazapine) which brings about its anti-anxiety/antidepressant effect⁶. Agomelatine is a restricted drug within Oxford Health. It is currently not recommended by NICE⁷ and is black listed by Oxfordshire and Buckinghamshire PCTs. For further information about this drug, please see Oxford Health Medicines Information Bulletin Vol 9 No 1 ([link](#)).

Suicide risk:

Antidepressant therapy has been associated with a short term increase in suicidal thoughts and acts, particularly in young adults and adolescents. It should be noted that although the relative risk might be elevated compared to placebo, the absolute risk remains very low¹. Secondly, the most effective way to reduce suicidality is to treat depression. Nevertheless, the risk of overdose should be considered when prescribing antidepressants. Drugs with lower toxicity (e.g. SSRIs) should be chosen and limiting tablet quantities may be necessary. Patients under 30 should be reviewed within 7 days. Depressed patients with insomnia have significantly higher suicidal ideation, so it is important to manage sleep disorders in the early stages of treatment³ (especially if the antidepressant can make insomnia worse).

Physical Health Checks:

All patients with severe mental illness have increased physical health risks which should be monitored at least yearly according to PCT good practice SMI monitoring guidelines. For further information see the trusts psychotropic monitoring guidelines ([link](#))

Referral to secondary care

Refer all patients with a history of mania or manic symptoms that might be suggestive of bipolar disorder. Refer patients who have a poor response to treatment, co-morbid substance misuse, intolerable side effects, non-adherence to treatment or other significant risk factors.

Patient information needs:

Provide verbal/written information about management of individual mental illness and discuss benefits/side effects of each drug. Discuss the gradual onset of action of antidepressants and advise about potential early adverse effects; e.g. insomnia, akathisia, suicidal ideation. Advise about withdrawal symptoms and possible interactions with other drugs. Highlight the symptoms of serotonin syndrome and advice on what to do if it develops.

Withdrawal symptoms:

All antidepressants have been associated with discontinuation symptoms - although patients should be informed they are not addictive. These include flu-like symptoms, nausea, irritability, neurosensory disturbances, etc. The onset is usually within 5 days of stopping treatment, depending on the half life of the drug. The risk is increased if patients miss or reduce doses and also with drugs that have a short half life e.g. paroxetine, venlafaxine, with children and adolescents and in those taking other psychotropic medication¹. Gradual withdrawal (over at least 4 weeks) is recommended to reduce this risk.

ANTIDEPRESSANTS RELATIVE SIDE EFFECTS (most are dose related)

(Adapted from Psychotropic Drug Directory 2010 and Maudsley Guidelines 10th edn.)

Drug	Anti - cholinergic	Cardiac	Nausea #	Sedation	Overdose §	Pro- convulsant	Sexual dysfunction
Tricyclics (TCA)							
Amitriptyline	●●●	●●●	●●	●●●	●●●	●●	●●
Clomipramine	●●●	●●	●●	●●	●	●●	●●●
Dosulepin	●●	●●	○	●●●	●●●	●●	●●
Doxepin	●	●●	●	●●●	●●	●●	●●
Imipramine	●●	●●	●●	●●	●●●	●●	●●
Lofepramine	●●	●	●	●	○	○	●●
Nortriptyline	●●	●	●●	●	●●	●	●●
Trimipramine	●●●	●●	●	●●	●●	●	●●
SSRIs							
Citalopram	○	○	●●●	○	●	○	●●
Escitalopram	○	○	●●	○	○	○	●●
Fluoxetine	○	○	●●	○	○	○	●●
Fluvoxamine	●	○	●●●	●	○	○	●
Paroxetine	○	○	●●	●	○	○	●●●
Sertraline	○	○	●●	○	○	○	●●
MAOI's							
Isocarboxazid	●●	●●	●●	●	●●	○	●
Phenelzine	●	●	●●	●	●●●	○	●
Tranylcypromine	●	●	●●	○	●●●	○	●
Others							
Agomelatine	○	○	○	●	○	○	○
Duloxetine	○	○	●●	○	?	?	●●
Mianserin	●	○	○	●●	○	○	●
Mirtazapine	○	○	○	●●●	○	●●	○
Moclobemide	●	○	●	○	○	?	●
Reboxetine	●	●	●	●	○	○	○
Trazodone	●	●	●●●	●●	●	○	●●
Venlafaxine	○	●●	●●	○	●●	●	●●

●●● = Marked effect ●● = Moderate effect ● = Mild effect ○ = Little or minimal effect

? = No information or little reported # = Typical serotonergic side-effect § = Based on UK Fatal Toxicity Index

SSRI-selective serotonin reuptake inhibitor MAOI-monoamine oxidase inhibitor SNRI-serotonin noradrenaline reuptake inhibitor

General information

•**SSRIs** commonly cause headache and gastrointestinal disturbances. They have a relatively higher propensity to cause sexual dysfunction (in particular erectile dysfunction), hyponatraemia and GI bleeds than other antidepressants.

•**Mirtazapine** commonly causes sedation, increased appetite and weight gain. It can also infrequently cause reversible blood dyscrasias, including agranulocytosis. FBC should be checked at any sign of infection.

•Overall **Venlafaxine** is better tolerated than TCAs but not SSRIs². It commonly causes dose-related increases in blood pressure and pre-existing hypertension should be controlled. Use with caution in patients with impaired cardiac function. There are no longer recommendations to restrict its use to specialist initiation however clinicians should be mindful of its potential cardiac adverse effects. Blood pressure monitoring is recommended after initiation of treatment and after dose increases⁵

•**Tricyclic antidepressants** have a higher burden of anti-cholinergic side effects (dry mouth, blurred vision, constipation) and cardiovascular effects (hypotension, tachycardia and QTc prolongation) than other antidepressants. Many of them also cause significant sedation.

For further information see special series bulletin "Antidepressants-Common Adverse Reactions" ([link](#))

References:

1. Taylor, D et al. The Maudsley Prescribing Guidelines 10th edition 2009. Informa Healthcare.
2. NICE CG 90 Depression Oct 2009 www.nice.org.uk
3. Bazire, S. Psychotropic Drug Directory 2010. Healthcomm.
4. Cipriani et al. Comparative efficacy and acceptability of 12 new generation antidepressants: a multi-treatment meta-analysis. The Lancet. 2009; 373:746-58
5. Wyeth pharmaceuticals. Summary of Product Characteristics for Efexor XL. Updated Oct 2010. www.medicines.org.uk
6. Servier Laboratories Ltd. Summary of Product Characteristics for Valdoxan. Updated Feb 2011. www.medicines.org.uk
7. NICE TA 231. Agomelatine for the treatment of major depressive disorders. July 2011