573FM.1 Depression in Adults and Older Adults: Oxford Health NHS FT and Primary Care Treatment Guidelines

Click here for link to:
2-page antidepressant treatment algorithm

Contents

1	Overview of pathway	Page
1.1	Assessment and diagnosis	2
1.2	Sub threshold / mild depression	2
1.3	Moderate / severe depression	3
2	**Antidepressant treatment**	
2.1	General principles	3
2.2	First line options	4
2.3	Second line options	5
2.4	Third line options	5
2.5	Fourth line options choice	8
3	**Stopping medication and discontinuation symptoms**	
3.1	Stopping medication	11
3.2	Onset	12
3.3	Symptoms	12
3.4	Management	12
4	**Switching antidepressants**	
4.1	General Principles	13
4.2	Strategies for common switches	14
5	**Relative side effects**	15
6	**Secondary care treatment**	
6.1	Criteria for referral to secondary care	15
6.2	Discharge from secondary care	16
7	**Special considerations – older adults**	
7.1	General principles	16
7.2	Medication choice	17
8	**Special considerations - pregnancy**	
8.1	General principles	18
8.3	Choice of antidepressant	19
9	**Special considerations – breast-feeding**	
9.1	General principles	21
9.2	Choice of antidepressant	22
10	**Special considerations – other populations**	
10.1	Epilepsy	23
10.2	Renal impairment	23
10.3	Coronary Heart Disease	23
11	**Resources for patients**	23
12	**References**	23
Appendix 1	Diagnostic criteria	25
Appendix 2	PHQ-9	26
Appendix 3	Suicide risk assessment	27
Appendix 4	Minimum effective antidepressant doses	27

1. Overview of pathway

1.1 Assessment and diagnosis

The tools below can be used to assess for subthreshold, mild/moderate or severe depression:

- Diagnostic criteria (**Appendix 1**)
- PHQ-9 (**Appendix 2**)
- Suicide Risk Assessment (**Appendix 3**)

1.2 Sub threshold/mild depression

Likely to benefit from low intensity psychological intervention. Patients can self-refer to psychological services (Improving Access to Psychological Services [IAPT]):

- Buckinghamshire: Healthy Minds Bucks – service information and patient self-referral link: https://www.oxfordhealth.nhs.uk/healthyminds/ or call 01865 901600
- Oxfordshire: Talking Spaces Plus – service information and patient self-referral link: https://www.oxfordhealth.nhs.uk/talkingspaceplus/ or call 01865 901 222

Antidepressants should not be used routinely to treat mild depression because the risk-benefit ratio is poor.

However, for people with persistent sub-threshold depressive symptoms or mild to moderate depression who have not benefitted from a low-intensity psychosocial intervention or have symptoms that have been present for a long period (typically at least 2 years), discuss the relative merits of different interventions with the person and provide as appropriate:

- An antidepressant
- A high intensity psychological intervention*
- Referral for further assessment and interventions

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High intensity psychological interventions

IAPT services (via Healthy Minds Bucks or Oxon Talking Space Plus) offer a stepped model of care from advice through to 1:1 therapy including high intensity psychological interventions. If a patient is not appropriate for IAPT (cluster 4 and above or complex presentation) then refer to AMHT, where psychological therapies are integrated

1.3 Moderate or severe depression

For people with moderate or severe depression, combination an antidepressant medication with a high-intensity psychological intervention (Cognitive Behavioural Therapy and Interpersonal Therapy) – see note about IAPT services above (*).

Refer to secondary care mental health services in severe depression or when moderate depression is either treatment-resistant** or poses a high risk of self-harm or self-neglect. For further information and other criteria for referral to secondary care, see section 6.

2. Antidepressant treatment

2.1 General principles

- Discuss choice of drug with the patient and provide written information as appropriate.
- For people started on antidepressants who are not considered to be at increased risk of suicide, normally see them after two weeks. See them regularly thereafter, for example at intervals of two to four weeks in the first three months, and then at longer intervals if response is good.
- Patients started on antidepressants who are at increased suicide risk and those younger than 30 years, should normally be seen after one week and frequently thereafter as appropriate until the risk is no longer considered clinically important.
- Titrate the dose (if necessary) to a recognised minimum effective dose (see table in appendix). Assess efficacy after two weeks.
- If no effect, assess weekly for a further two weeks. If still no response, consider increasing the dose. If still no effect switch to a different antidepressant.
- If no effect to a second treatment**, consider alternative treatment options or refer to secondary care for further advice.
- For a single episode, continue treatment for at least 6-9 months after resolution of symptoms.
- Patients with two prior episodes and functional impairment should be treated for at least two years. After two years, patients should be reassessed and the risks and benefits of continuing maintenance treatment beyond two years weighed up. In some cases, life-long antidepressant treatment may be considered appropriate.
- Withdraw antidepressants gradually; always inform patients of the risk and nature of discontinuation symptoms.

****Treatment resistant depression.**

Whilst there is no universal consensus definition, treatment resistant depression is widely accepted to be a failure to respond to separate, adequate trials (dose and duration) of two antidepressants.

2.2 First line options

- Restart a previously effective antidepressant if appropriate, OR choose from the options below, taking into account any factors that might affect choice.
- Choice should include patient preference if possible.
- Approximately, one-third of patients do not respond to the first antidepressant that is prescribed.

Treatment option (listed alphabetically)	**Drug class**	**Notes**	**Traffic light status**	**Drug Tariff cost** (per month at minimum effective dose – see appendix 4)
Citalopram	SSRI	One of the least likely SSRIs to cause *pharmacokinetic* drug interactions. However, citalopram is contraindicated in patients with known QT interval prolongation and those taking other medicines known to prolong the QT interval. Maximum licensed doses were lowered in 2011. For further information refer to: Oxford Health MI Bulletin.	Green	£1.07
Mirtazapine¥	Other - presynaptic α2-antagonist	SSRIs are generally considered to be the first line option, however mirtazapine may be considered as a first-line option if the sedative effects would be particularly beneficial, or where concomitant medical conditions or concurrent medication make an SSRI less suitable (e.g. increased risk of bleeding). Mirtazapine can also be considered if a patient experiences SSRI-related adverse effects (GI bleeding, sexual dysfunction, insomnia). Mirtazapine is not associated with nausea (high incidence with SSRIs). It has a high incidence of causing weight gain. It is more sedating at the lower end of the dose range.	Green	£2.64
Sertraline¥	SSRI	Evidence of good overall tolerability although associated with a slightly higher incidence of diarrhoea than other SSRIs. Sertraline is often the SSRI of choice where there are co-morbid physical health problems (e.g. ischaemic heart disease, epilepsy)	Green	£1.55
Escitalopram¥ may be used 1st line by specialists treating	SSRI	One of the least likely SSRIs to cause *pharmacokinetic* drug interactions. However, escitalopram is contraindicated in patients with known QT interval prolongation and those taking other medicines known to	Green	£2.03

severely ill patients. In primary care, escitalopram is restricted to use as a 2nd line treatment option.		prolong the QT interval. For further information refer to: Oxford Health MI Bulletin.		

¥ Escitalopram, mirtazapine, paroxetine, agomelatine, and sertraline had a relatively higher response and lower dropout rate than other antidepressants in the most comprehensive analysis of comparative efficacy and acceptability of antidepressants for depression to date (Cipriani 2018).

2.3 Second line options

- Switch to a different antidepressant from the list below, taking into account any factors that might affect choice.
- There is marked inter-individual variability in tolerability and many patients who poorly tolerate one SSRI will tolerate another.

Treatment option (listed alphabetically)	**Drug class**	**Notes**	**Traffic light status**	**Drug Tariff cost (per month at minimum effective dose – see appendix 4)**
Citalopram	SSRI	See notes above		
Escitalopram	SSRI	See notes above		
Fluoxetine	SSRI	Long half- life. High risk of drug interactions due to CYP2D6 inhibition. May make a good choice if concerned about discontinuation symptoms or if relatively poor compliance is likely.	Green	£1.04
Mirtazapine	Other - presynaptic α2-antagonist	See notes above		
Sertraline	SSRI	See notes above		

2.4 Third line options

- An antidepressant from the options below might be being selected because antidepressants from the first- and second-line options have been poorly tolerated or are relatively contraindicated and not necessarily because of poor response. In this situation, if the patient is being treated in primary care, one of the green traffic light options may be prescribed, if appropriate.
- If there has been poor response following adequate trials (dose and duration) of two previously prescribed antidepressants, at this stage, if the patient is being treated in primary care, one of the green traffic lighted options may be prescribed if considered

appropriate. Otherwise, consideration should be given to referring patients with treatment resistant depression to secondary care – see section 6.

- Switch, augment or combine, taking into account any factors that might affect choice.

Treatment option (listed alphabetically) – switch to:	**Drug class**	**Notes**	**Traffic light status**	**Drug Tariff cost (per month at minimum effective dose – see appendix 4)**
Duloxetine	SNRI	May be useful in patients with neuropathic pain. Avoid in uncontrolled hypertension.	Green	£2.77
Mirtazapine¥	Other - presynaptic α2-antagonist	if not already used as a 1st or 2nd line treatment. Can also be used to augment an SSRI used as 1st or 2nd line treatment where partial benefit has been obtained. See also additional notes in section 2.2 above.	Green	£2.64
Venlafaxine	SNRI	Prominent discontinuation symptoms. Avoid, if at risk of arrhythmia or in uncontrolled hypertension. For dual effect as a serotonin and noradrenaline reuptake inhibitor doses greater than 150mg/d are necessary. Greater risk in overdose than most SSRIs.	Green	£2.60
Vortioxetine	Other – potent serotonin reuptake inhibitor	Vortioxetine is recommended by NICE [TA367] as an option for treating major depressive episodes in adults whose condition has responded inadequately to two antidepressants within the current episode. It is a more costly option than other third choice options.	Amber – can be initiated in primary care on advice of specialist	£27.72
Treatment option (listed alphabetically) – augment/combine:	**Drug Class**	**Notes**	**Traffic Light status**	**Drug Tariff cost (per month at minimum effective dose – see appendix 4)**
Add lithium		Recommended by NICE. Lithium should only be initiated in secondary care but a request to share care is appropriate when the patient is on a stable dose and is mentally well. Refer to OH NHSFT lithium shared care	Amber shared care	e.g. at 800mg/d → add £2.25

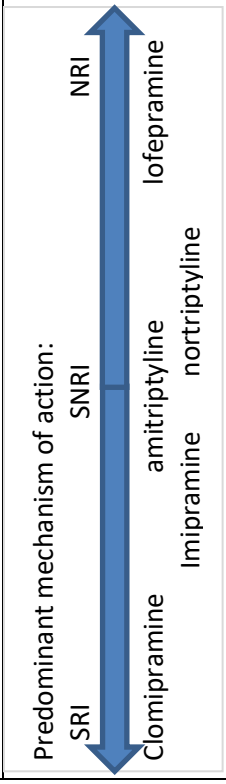
		protocols (Oxfordshire / Buckinghamshire)		
Add second generation antipsychotic		Recommended by NICE. NICE guideline CG90 suggests aripiprazole, quetiapine, olanzapine, or risperidone. Augmentation or combination treatment should only normally be started in primary care in consultation with a psychiatrist. Combined treatments are associated with a higher side effect burden and may require additional monitoring. Please refer to OH NHSFT antipsychotic physical health monitoring guidelines (Oxfordshire / Buckinghamshire)	Amber – initiation by specialist with ongoing treatment in primary care	+aripiprazole 5-20mg/day → add £1.37 - £2.86 +quetiapine 150-300mg/ day → add £2.22 – £3.23 +risperidone 0.5-3mg/day → add £2.40 - £3.33 +olanzapine 5-12.5mg/ day → add £1.75 - £3.80
SSRI or SNRI plus mirtazapine¥		Recommended by NICE. Combined treatments are associated with a higher side effect burden and may require additional monitoring.	Green	Add £2.64
SSRI plus trazodone	Other – increases NA and 5HT turnover	Very sedating. Trazodone has a lower efficacy and tolerability profile when compared with other antidepressants as monotherapy (Cipriani 2018). Therefore, use as monotherapy should be avoided in preference for other more effective treatments where possible. However, it has been included here as it may have a role as an adjunct if insomnia or anxiety are significant co-morbid, complicating factors in the presentation.	Green	Add £4.14

¥ Escitalopram, mirtazapine, paroxetine, agomelatine, and sertraline had a relatively higher response and lower dropout rate than other antidepressants in the most comprehensive analysis of comparative efficacy and acceptability of antidepressants for depression to date (Cipriani 2018).

2.5 Fourth line options

- At this stage, choices include antidepressants or augmentation strategies listed under previous steps that have not already been tried, or a choice from the antidepressants or augmenting medication listed below, but also refer to the notes, traffic light status and prescribing restrictions.

Treatment option (listed alphabetically) – **switch to:**	**Drug class**	**Notes**	**Traffic light status**	**Drug Tariff cost** (per month at minimum effective dose – see appendix 4)
Agomelatine¥	Other - melatonergic agonist and 5-HT_{2C} antagonist	Agomelatine has been associated with rare cases of liver injury and requires regular monitoring of LFTs for the first 24 weeks of treatment (and for 24 weeks following a dose increase) - see liver monitoring scheme. Agomelatine should only be prescribed after carefully evaluating risk factors for hepatic injury – see prescriber's guide. It is restricted for use in patients who have been unable to tolerate other antidepressant treatment options because of weight gain, sexual dysfunction, or severe gastrointestinal adverse effects. It may also be considered for patients where sleep is particularly problematic, only where other sedating treatment options have not been helpful.	Amber – initiation by specialist with ongoing treatment in primary care. Patients should remain under the care of an Oxford Health specialist until all scheduled LFT monitoring is complete and results are normal (minimum of 24 weeks, or for 24 weeks from the date of a dose increase). Only at this point, and only if the patient is well, should a patient be discharged back to GP care.	£29.58
Moclobemide	Reversible inhibitor of	Reduced risk of hyponatraemia and sexual adverse effects	Amber – initiation by specialist with	£13.99

	monoamine oxidase A (RIMA)	than SSRIs. Fewer dietary restrictions than traditional MAOIs.	ongoing treatment in primary care	
MAOI	Monoamine oxidase inhibitor (MAOI)	**Phenelzine = 1st choice,** Dietary restrictions and drug interactions.	Amber – initiation by specialist with ongoing treatment in primary care	Phenelzine £18.90 Tranylcypromine £735.24 Isocarboxazid £350.14
Tricyclic antidepressants – see notes	Tricyclic antidepressant (TCA) 	Do not newly initiate **trimipramine** or **nortiptyline** due to their very high costs. Side effect profiles of TCAs differ. Some TCAs are more sedative than others (sedative – **amitriptyline**, **clomipramine**; less sedative – **imipramine**, **lofepramine**). All TCAs have anticholinergic side-effects, but the extent varies, and all are potentially cardiotoxic in overdose apart from **lofepramine,** which is considered the safest TCA, if there is a risk of overdose. **Dosulepin**	Amber – on specialist recommendation: clomipramine, imipramine, lofepramine Amber – existing patients who can't be swapped to a more cost-effective alternative: nortiptyline, trimipramine Amber – existing patients and exceptional cases where safer alternatives are not suitable: amitriptyline	Clomipramine £11.10 Imipramine £17.12 Lofepramine £22.67 Nortriptyline £75.52 Trimipramine £435.00

		should not be prescribed due to high toxicity risk in overdose. **Amitriptyline** is also highly toxic in overdose. If no suitable safer alternative exists, patients currently prescribed amitriptyline may continue treatment and it should only be started in new patients as an exception where risks and benefits have been considered.	Non-formulary: dosulepin	
Treatment option – augment/combine:	**Drug class**	**Notes**		
Bupropion monotherapy OR SSRI or SNRI plus bupropion	Noradrenaline and dopamine reuptake inhibitor	In the US, bupropion is licensed as monotherapy and as an augmentation to antidepressant treatment. In the UK, use is off-label for these indications. This must be discussed with the patient and documented. Bupropion may be used to augment Combined treatments are associated with a higher side effect burden and may require additional monitoring. Bupropion has a low risk of sexual dysfunction and weight gain and may be a beneficial option when these problems	Red – restricted to consultant initiation only. Only prescribe bupropion where all other options have been excluded. Prescribing MUST be retained by secondary care.	Monotherapy: £38.98 Combined: SSRI or SNRI plus £38.98

		have occurred with other antidepressants.		
Add liothyronine	Thyroid hormone	Specialist prescribing in exceptional cases only, following OH DTG approval. TFT monitoring required. Very high cost drug. Subject to NHS England guidance on use.	Red – restricted to consultant only initiation. Also see notes. Contact the OH DTG by email to make an application to use liothyronine. Prescribing MUST be retained by secondary care.	Liothyronine 20 to 50mcg/day → add £161.36 to £470.72

A note on reboxetine: Reboxetine has not been included as a routine treatment option in this guideline. It has been shown to have a lower efficacy and tolerability profile when compared with other antidepressants (Cipriani 2018) and a high degree of publication bias and outcome reporting bias has been noted (Edying 2010). Therefore, use should be avoided in preference for other more effective treatments. At the time of publication of this updated OH guideline, it is likely that there are a small number of patients already prescribed reboxetine. Where efficacy in an individual has been clearly demonstrated, prescribing may continue and it should be treated as an amber traffic light status, with initiation by specialist and continuation in primary care.

¥ Escitalopram, mirtazapine, paroxetine, agomelatine, and sertraline had a relatively higher response and lower dropout rate than other antidepressants in the most comprehensive analysis of comparative efficacy and acceptability of antidepressants for depression to date (Cipriani 2018).

3. Stopping medication and discontinuation symptoms

3.1 Stopping medication

In general, when a plan is made to stop antidepressant medication this should be done gradually to help reduce the risks of relapse and of discontinuation symptoms (unless a serious adverse effect has occurred).

Providing a detailed explanation to the patient of what to expect when stopping an antidepressant may help to achieve a successful discontinuation.

Discontinuation symptoms can usually be avoided or minimised by tapering the dose down and discontinuing treatment over at least four weeks. This is more important for drugs with a short half-life and is not required with fluoxetine (unless doses used are greater than 20mg daily).

A patient information leaflet about stopping antidepressants is available here and additional specific leaflets in section 3.4 below.

Discontinuation symptoms

3.2 Onset

Onset is usually within 5 days of stopping treatment (depending on the half-life of the antidepressant) or occasionally during taper or after missed doses (short half-life drugs only).

3.3 Symptoms

Anyone can experience discontinuation symptom. The risk is increased with drugs with a short half-life e.g. paroxetine, venlafaxine and when an antidepressant has been taken for longer than six weeks.

Symptoms can vary in form and intensity. They are usually mild and self-limiting lasting only a week or two but can occasionally be severe and prolonged in some cases. Symptoms include; flu-like symptoms, 'shock-like' sensations, dizziness exacerbated by movement, restlessness, insomnia, sweating, excessive (vivid) dreaming, irritability, crying spells.

3.4 Management

To reduce the risk of discontinuation symptoms occurring, antidepressants should be tapered out gradually. This is particularly important for antidepressants with a short half-life (e.g. paroxetine, venlafaxine) and less so for those with a long half-life (e.g. fluoxetine, which does not need tapering below a dose of 20mg daily).
The following general recommendations relate to stopping an antidepressant. If the plan is to switch from one antidepressant to another, see section 4 below for guidance.

In general, tapering the dose gradually over a minimum period of four weeks is recommended. Some people may require longer periods, particularly with drugs with a shorter half-life. Tell the person that discontinuation symptoms may appear and provide information about what to expect (see leaflets below, which may support discussions). If someone reports discontinuation symptoms and they are:

Mild: monitor and provide reassurance.

Severe: consider reintroducing the original antidepressant at the dose that was effective (or another antidepressant with a longer half-life from the same class, if appropriate), and reduce the dose gradually while monitoring symptoms.

Information leaflets for patients:

Coming off mental health medicines
Stopping or coming off antidepressants
Stopping or coming off citalopram
Stopping or coming off escitalopram
Stopping or coming off fluoxetine
Stopping or coming off sertraline

4. Switching antidepressants

4.1 General principles

- All antidepressants have the potential to cause withdrawal symptoms when taken continuously for 6 weeks or longer. Symptoms include; flu-like symptoms, 'shock-like' sensations, dizziness exacerbated by movement, insomnia, excessive (vivid) dreaming, irritability, crying spells
- Antidepressants should not be stopped abruptly unless a serious adverse event has occurred.
- The speed at which antidepressants are switched is best judged by monitoring patient tolerability. No clear guidelines applicable to all are available, so caution is required, and the regimen tailored individually.
- The co-administration of some antidepressants, even when switching is contra-indicated e.g. MAOIs and SSRIs; MAOIs and TCAs.
- In some cases, switching can be straight forward to carry out. For example, when switching from one SSRI (**not** including fluoxetine) to another SSRI a direct switch can take place. The effects may be similar enough for the second drug to counteract the withdrawal effects of the first.
- Potential dangers of simultaneously administering two antidepressants can include serotonin syndrome, hypotension, drowsiness, and elevation of tricyclic plasma levels by certain SSRIs.
- Serotonin syndrome symptoms include restlessness, diaphoresis, tremor, sweating, myoclonus, confusion, convulsions and death.
- Provide information on serotonin syndrome as appropriate. A printable patient leaflet is available here.

4.2 Strategies for common switches

[Table adapted from The Maudsley Prescribing Guidelines in Psychiatry. 13th edition]

To / **From**	Fluoxetine	Other SSRIs (not fluoxetine), vortioxetine	SNRIs (duloxetine, venlafaxine)	Mirtazapine	TCAs (except clomipramine)
Fluoxetine		Gradually **taper** to 20mg and **stop, wait** 4-7 days and then start SSRI at low dose.	Gradually **taper** to 20mg and **stop, wait** 4-7 days and then start SSRI at low dose.	**Cross taper**: gradually taper the dose to 20mg and stop. At the same time as tapering, start mirtazapine and increase dose cautiously.	Gradually **taper** to 20mg and **stop, wait** 4-7 days and then start low dose TCA.
Other SSRIs (not fluoxetine), vortioxetine	**Direct switch possible**: stop SSRI/vortioxetine one day and start fluoxetine the next.	**Direct switch possible**: stop SSRI/vortioxetine one day and start next SSRI the next.	**Direct switch possible**: stop SSRI/vortioxetine one day and start SNRI the next.	**Cross taper**: gradually taper the dose and stop. At the same time as tapering, start mirtazapine and increase dose cautiously.	**Cross taper**: gradually taper the dose and stop. At the same time as tapering, start a low dose of TCA and increase cautiously.
SNRI (duloxetine, venlafaxine)	**Direct switch possible**: stop SNRI one day and start fluoxetine the next.	**Direct switch possible**: stop SNRI one day and start SSRI/ vortioxetine the next.	**Direct switch possible**: stop one SNRI one day and start the next SNRI the following day.	**Cross taper**: gradually taper the dose and stop. At the same time as tapering, start mirtazapine and increase dose cautiously.	**Cross taper**: gradually taper the dose and stop. At the same time as tapering, start a low dose of TCA and increase cautiously.
Mirtazapine	**Cross taper**: gradually taper the dose and stop. At the same time as tapering, start fluoxetine and increase dose cautiously.	**Cross taper**: gradually taper the dose and stop. At the same time as tapering, start SSRI/ vortioxetine and increase dose cautiously.	**Cross taper**: gradually taper the dose and stop. At the same time as tapering, start SNRI and increase dose cautiously.		**Cross taper**: gradually taper the dose and stop. At the same time as tapering, start mirtazapine and increase cautiously.
TCAs (except clomipramine)	**Halve TCA dose**, **add** fluoxetine and **continue slow taper** of TCA	**Halve TCA dose**, **add** SSRI / vortioxetine and **continue slow taper** of TCA	**Cross taper**: gradually taper the dose and stop. At the same time as tapering, start a low dose of SNRI and increase cautiously.	**Cross taper**: gradually taper the dose and stop. At the same time as tapering, start mirtazapine and increase cautiously.	**Direct switch possible**: stop TCA one day and start the next TCA the following day.

Further information and guidance can be found at the following links:

How do you switch between MOAIs and SSRIs, TCAs or related antidepressants?

How do you switch between TCAs, SSRIs and related antidepressants?

5. Relative side effects

- Anticholinergic: TCAs have marked anticholinergic properties compared to SSRIs, SNRIs and mirtazapine. Combining several drugs with anticholinergic activity increases the anticholinergic cognitive burden (ACB) for an individual. A high ACB score has been reported to increase the risk of cognitive impairment, death and dementia.
- Cardiac: TCAs (except lofepramine) have marked cardiac effects compared to SSRIs and mirtazapine.
- Nausea: SSRIs (especially fluvoxamine) have marked effects, as do some TCAs. Mirtazapine has no effect.
- Sedation: Some TCAs, mirtazapine and trazodone have a marked effect. SSRIs and SNRIs have minimal effect.
- Sexual dysfunction: SSRIs, amitriptyline, clomipramine, imipramine, venlafaxine and duloxetine have marked effects. Mirtazapine, agomelatine, vortioxetine, and moclobemide have minimal effects.

6. Secondary care treatment

6.1 Criteria for referral to secondary care

Consider referring when:

- Depression is severe.
- Patients have a history of mania or manic symptoms, or bipolar disorder is suspected.
- Psychotic symptoms are present.
- Risks are significant (suicide, self-neglect).
- There is a possibility of dementia.
- There is significant co-morbid substance misuse – encourage patients to also self-refer to local Drugs & Alcohol services:
    - Buckinghamshire: https://onerecoverybucks.org/
    - Oxfordshire: https://www.oxfordshiredaat.org/2012/OxDandAServices.htm
- There is a poor response to two adequate (dose and duration) trials of medication.

Support may be able to be provided by the Community Mental Health Team (CMHT) for complex cases or patients that are at risk.

Advice from secondary care about medication could be by telephone or by email.

6.2 Discharge from secondary care

Patients must only be discharged back to primary care if they are prescribed a green or amber traffic-lighted medication. The discharge letter must include a treatment plan with details such as the anticipated duration of treatment, any necessary monitoring, guidance about when and how to withdraw treatment, and what to do should symptoms re-emerge at any time after discharge or during a planned withdrawal of medication.

7 Special considerations – older adults

7.1 General principles

- There is no single best antidepressant for use in the elderly.
- Changes in distribution, metabolism and excretion of drugs changes as the body ages.
- Older people are more susceptible to side effects of medication, particularly centrally acting medicines.
- Response to antidepressant medication often takes longer than in adults.
- There is a higher incidence of physical health conditions in the older population, which may influence drug choice.
- Patients are often on more concomitant medication and are at an increased risk of drug interactions.
- SSRIs are often used first line and may be better tolerated than other antidepressants, but the risk of hyponatraemia and bleeding increases with age. Fluoxetine has a very long half-life and significantly more drug interactions, so alternatives such as sertraline, citalopram or escitalopram may be preferred.
- Some TCAs are strongly anticholinergic and could affect cognition, unmask Alzheimer's disease, and cause urinary retention. Some also cause orthostatic hypotension and sedation.
- Antidepressant use in the elderly may increase the risk of falls.
- Start with a low dose and increase cautiously.
- Avoid treating the adverse effects of antidepressants with another medication. Ideally, switching to a better tolerated alternative is preferred where possible.

7.2 Medication choice

For recommendations in patients with renal impairment or cardiovascular disease, see section 10 (special populations – other).

Preferred 1st line/ 2nd line	**Notes**
Sertraline, citalopram, escitalopram	Consider risk of bleeding and the potential need for a PPI. Citalopram and escitalopram can increase the QTc interval – see section 2 above for more information.
Alternative options	**Notes**
Mirtazapine	May also make a good first line choice if the patient takes warfarin* / is at significant risk of bleeding or if sleep is a major issue. **Caution should still be applied to concomitant use of warfarin, as there are conflicting reports of the potential for minor increases in INR at higher mirtazapine doses. Whilst the small increases are generally not considered clinically relevant, the manufacturer recommends close INR monitoring.*
Duloxetine and venlafaxine	Refer to notes in section 2 for place in therapy. Can also increase the risk of bleeding. Venlafaxine has a high risk of discontinuation symptoms due to its very short half-life.
Vortioxetine	For third line use in line with NICE TA – see above for place in therapy.
Agomelatine	Refer to notes in section 2 for place in therapy.
Trazodone	Very sedating. See notes in section 2 for place in therapy and note lower efficacy and tolerability profile.
Lofepramine	Mode of action is predominantly via noradrenaline reuptake – may therefore make a good alternative choice when serotonergic adverse effects need to be avoided or when an SSRI/ SNRI has caused hyponatraemia.
SSRI or SNRI plus mirtazapine	See notes in section 2.
Add lithium	See notes in section 2. Consider renal function and interacting medication such as diuretics, ACE inhibitors, NSAIDs etc.
Add second generation antipsychotic	See notes in section 2. Also consider the relative risks of using antipsychotics in older adults e.g. increased cerebrovascular adverse event risks, mobility and venous thromboembolism risks, and their relative sedative, metabolic, anticholinergic and cardiovascular effects.
TCAs (other than lofepramine) and MAOIs	With great caution and where other safer options are not suitable. See as per section 2 above.

8 Pregnancy

Seek specialist advice where appropriate. Refer to the commissioned perinatal service pathways:

- Oxfordshire [link pending] – see: contact details and how to refer
- Buckinghamshire

8.1 General principles

- Perinatal depression is common and can bring significant risk to the mother and baby.
- Not adequately treating antenatal depression is a risk to both the mother and the unborn baby. Risks include poorer pregnancy outcomes (premature birth, low birth weight, intra-uterine growth retardation), adverse child development outcomes, adverse consequences of deliberate self-harm (to mother and baby), and there is an increased risk of postnatal depression.
- Establishing response to any previously used antidepressant medication is a key factor to consider when determining choice during pregnancy.
- Choose the antidepressant with the lowest risk profile for the woman, foetus and baby, taking into account a woman's previous response to medication.
- Medication choice may also be influenced by the stage of pregnancy.
- Use the lowest effective dose but ensure the use of subtherapeutic doses is avoided.
- Use monotherapy wherever possible.
- Stopping medication suddenly without giving careful holistic consideration to the risks and benefits, is not in the best interests of the mother/developing baby.
- Discontinuing antidepressants during pregnancy may be associated with rates of depressive relapse of up to 70%.
- The risks associated with a relapse or an inadequately treated mental illness may be greater than the risk of using medication in pregnancy.
- It is often best to continue with an antidepressant already in use during pregnancy that is keeping the mother well, rather than trying to change to a different one just because it has a relatively larger amount of safety data.
- Inform the mother that the background pregnancy risks in the general population are:
    - Spontaneous major malformation rate – 2 to 4%
    - Spontaneous miscarriage rate – 10-20%
- Antidepressant use in the third trimester is associated with neonatal adaptation syndrome in the baby. Symptoms can include sleeping problems, tremors, constant crying, suckling problems, and myoclonus. Risk differs according to which antidepressant is used, but generally symptoms are mild and self-limiting.
- Provide balanced information to the mother (and partner family, carer as appropriate) about the potential benefits of psychological interventions and psychotropic medication, the possible consequences of no treatment, the possible

harms associated with treatment, what might happen if treatment is changed or stopped, particularly if psychotropic medication is stopped abruptly.

- Information leaflets about medication in pregnancy, produced by the UK Teratology Information Service, are available at BUMPS (Best Use of Medicines in Pregnancy): https://www.medicinesinpregnancy.org/
- Consider the mother's wishes and plans for breastfeeding at an early stage and the potential implications of medication use during this period – see breastfeeding section below.
- Document all discussions and decisions.

Perinatal Mental Health contact and referral details:

- Oxfordshire: https://www.oxfordhealth.nhs.uk/oxfordshire-perinatal-service/referrals/
- Buckinghamshire: https://www.oxfordhealth.nhs.uk/buckinghamshire-perinatal-mental-health-service/professionals/

8.2 Choice of antidepressant*

Antidepressants* considered to be of lower risk and which may be preferred in new episodes of depression: ***Must be considered in conjunction with principles above and information below.***
Sertraline (best choice if the mother plans to breast feed) Fluoxetine Citalopram Escitalopram

Some studies have found that antidepressant use in pregnancy might be associated with adverse outcomes. A summary is included below:

SSRIs Widely prescribed in pregnancy and best studied class of antidepressant.	*Cardiac malformations:* There are unproven and conflicting reports about a possible association with an increased risk of cardiac malformations (ventricular and atrial septal defects) to a rate of 2 in 100 from a background rate of 1 in 100. Large meta-analysis have failed to confirm this association.
	Persistent pulmonary hypertension of the new-born (PPHN): An association between SSRI use beyond 20 weeks of pregnancy and PPHN is possible but remains unclear. The first studies which identified an association between prenatal SSRI exposure and PPHN suggested that the risk was considerably higher (a 6-fold increase) than the background rate of 0.1-0.2%. Subsequent studies with large sample sizes indicate that the risk is smaller and more in keeping with the background rate (a 1.5-fold increase to about 0.3%). This was no longer significant when confounders were taken into

	account. Therefore, if risk is present, the absolute risk is very low, but this is a potentially serious neonatal complication.	
	Stillbirth or neonatal death: Limited data find no association.	
	Spontaneous abortion, low birth weight, and preterm delivery; Conflicting data. Association with an increased risk remains unclear.	
	Autistic Spectrum Disorder Around one in every 100 children develop ASD, regardless of whether their mother took any medicines in pregnancy. There is conflicting evidence for a small increased risk of autism with serotonergic antidepressant use. Some studies suggest an association between underlying maternal condition and ASD, but further study is warranted. The National Teratology Information Service currently states that data regarding risk of autism following in utero exposure to SSRIs are conflicting and potentially confounded and further studies are necessary before conclusions can be made.	
TCAs e.g. amitriptyline, imipramine, nortriptyline. Widely used during pregnancy over several decades but fewer specific published data available than for SSRIs (for clomipramine refer to possible risks with SSRIs above)	*Malformations*: The available data provides no strong evidence of an association between maternal use of TCAs as a class during pregnancy and an increased risk of congenital malformation overall, or of any specific malformations. However, data on individual TCAs is limited or absent and therefore it is not possible to rule out a risk.	
	Preterm delivery, preeclampsia, C Section deliveries, low Apgar scores: Unconfirmed associations of increased risk reported.	
	Persistent pulmonary hypertension of the new-born (PPHN): No reports of PPHN but theoretical concerns may exist.	
	ASD: Association unclear – conflicting evidence.	
Other antidepressants Limited exposure /outcome data – difficult to draw conclusions	SNRIs (venlafaxine and duloxetine)	Relatively limited data. *Malformations:* A possible association with cardiac defects may exist (as for SSRIs – see above) *Spontaneous abortion, low birth weight, and preterm delivery:* inconsistent data for miscarriage and preterm birth. *Persistent pulmonary hypertension of the new-born (PPHN):* theoretical risk of PPHN. Effects of venlafaxine on neurodevelopment not widely studied.
	Mirtazapine	*Malformations:*

		Limited data do not suggest a significantly increased risk of malformations but are too limited to exclude any increase in risk. *Spontaneous abortion, low birth weight, and preterm delivery:* conflicting data on risk of spontaneous abortion and preterm delivery. *Persistent pulmonary hypertension of the new-born (PPHN):* risk of PPHN is unknown. Neurodevelopmental effects of mirtazapine have not been studied.

*NB: No antidepressant has a marketing authorisation for use in pregnancy.

For further information and advice contact your local Perinatal Mental Health Service (Oxon; Bucks) or OH NHSFT Medicines Advice Service on 01865 904365.

9 Breast feeding

Seek specialist advice where appropriate. Refer to the commissioned pathways within Oxfordshire and Buckinghamshire's perinatal services (as above in section 8).

9.1 General principles

- Use a drug only when clearly indicated.
- Assess benefits & risks to mother and child.
- Prescribe at the lowest effective dose for the shortest required time.
- Avoid new drugs if possible, as there is likely to be less safety data.
- Avoid drugs that are known to cause serious toxicity in adults.
- Take particular care with new-borns, and don't expose premature babies to medication through the milk.
- Do not expose babies of very low birth weight (<2500g) or with medical conditions of their own to medication through the milk.
- Choose drugs with shorter half-lives in preference to those with longer half-lives where possible.
- Avoid drugs with active metabolites (drugs with long half-lives or active metabolites may accumulate in the milk and increase the risk of adverse effects).
- Avoid polypharmacy if possible, especially where drugs may have additive side effects.
- Monitor the infant closely for any unusual effects and for developmental milestones.

9.2 Choice of antidepressant

When assessing the risks and benefits of antidepressants for women who are breastfeeding or who are planning to breastfeed, take into account:

- The limited data about the safety of these drugs. The group of antidepressants with the most accumulated safety data are the SSRIs.
- Current or previous antidepressant treatment and response:
    - it is usually advisable to continue with the medication that has been effectively used during pregnancy
    - if a woman has not taken an antidepressant during pregnancy it is usually advisable to restart an antidepressant used previously if it was known to be effective.
- The risks associated with switching from a previously effective medication, in particular switching immediately after delivery, which is already a risky time for relapse – switching is usually not recommended.

Antidepressants* considered to be of lower risk and which may be preferred in new episodes of depression: ***Must be considered in conjunction with principles above and information below.***	
Sertraline Paroxetine	*Because of shorter half-lives, lower passage into milk and larger pools of data, paroxetine or sertraline are the preferred SSRIs for use in lactation.*
Imipramine	*No adverse effects have been noted in breastfed infants exposed to tricyclic antidepressants via breast milk (except for doxepin).* *Non-sedating TCAs are preferred, if clinically indicated.*

Links to question and answer documents produced by UK Medicines Information Service for NHS Healthcare Professionals:

Safety in Lactation: Antidepressants

SSRIs: Management of depression in breastfeeding mothers – are selective serotonin reuptake inhibitors (SSRIs) safe?

Tricyclic antidepressants: Management of depression in breastfeeding mothers – are tricyclic antidepressants safe?

Others: Management of depression in breastfeeding mothers – Are reboxetine, venlafaxine, duloxetine, mirtazapine, agomelatine and MAOIs safe?

*NB: No antidepressant has a marketing authorisation for use in breast-feeding.

For further information and advice contact your local Perinatal Mental Health Service (Oxon; Bucks) or OH NHSFT Medicines Advice Service on 01865 904365.

10 Special populations – other

10.1 Epilepsy

General guidance can be found here, but further specialist advice may need to be sought for individual cases: https://www.sps.nhs.uk/articles/what-is-the-most-appropriate-antidepressant-to-use-in-patients-with-epilepsy/

10.2 Renal impairment

General guidance can be found here, but further specialist advice may need to be sought for individual cases: https://www.sps.nhs.uk/articles/what-is-the-first-choice-antidepressant-for-patients-with-renal-impairment/

10.3 Coronary heart disease

General guidance can be found here, but further specialist advice may need to be sought for individual cases: https://www.sps.nhs.uk/articles/what-is-the-antidepressant-of-choice-in-coronary-heart-disease-chd/

11 Resources for patients

Patient information on mental health conditions, treatments and medication, including leaflets in several languages: Choice and Medication

Useful contacts and websites include:

- Oxford Health Mental Health Helpline: 0800 783 0119 or 01865 904 997
- MIND — www.mind.org.uk.
- Depression Alliance — www.depressionalliance.org.
- Depression UK — www.depressionuk.org.
- Mental Health Foundation — www.mentalhealth.org.uk.
- Out of hours: 111
- Samaritans: 116 123
- SaneLine: telephone helpline: 0845 767 8000. Open from 6pm to 11pm every day of the year.

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See also:
Guideline 572FM Antidepressant Treatment Algorithm

Title of Guideline	Depression in Adults and Older Adults: Oxford Health NHS FT and Primary Care Treatment Guidelines
Guideline Number	573FM
Version	1
Effective Date	February 2021
Review Date	February 2024
Original Version Published	February 2021
Approvals:	
Oxford Health Drugs & Therapeutics Group	November 2020
Area Prescribing Committee of Oxfordshire	November 2020
Buckinghamshire Medicines Value Group	November 2020
Medicines Check (Pharmacy)	1st February 2021
Clinical Guidelines Group	16th February 2021
Author/s	Rachel Hogan, Clinical Lead Pharmacist, Oxford Health NHS Foundation Trust
SDU(s)/Department(s) responsible for updating the guideline	Pharmacy, Oxford Health NHS Foundation Trust
Uploaded to Intranet	23rd February 2021
Buckinghamshire Healthcare NHS Trust	

Appendix 1: Diagnostic Criteria for Depression (CKS)

There are two classification systems used for diagnosing depression: the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) or the 11th revision of the International Classification of Diseases (ICD-11).

The NICE guideline, which is currently under review, refers to previous versions of these diagnostic criteria. NICE uses the DSM-IV criteria in preference to ICD-10 criteria as it is used in nearly all the evidence reviewed and it provides definitions for atypical symptoms and seasonal depression. Diagnosing depression using DSM-5 criteria:

- **Be alert to possible depression,** particularly in people with a history of depression or a chronic physical health problem with associated functional impairment.
- **Consider asking the person about the two 'core' symptoms of depression. Ask:**
  - During the last month have you often been bothered by feeling down, depressed, or hopeless?
  - Do you have little interest or pleasure in doing things?
- **If at least one of the two 'core' symptoms have been present most days, most of the time, for at least 2 weeks, ask about:**
  - **Associated symptoms of depression:**
    - Disturbed sleep (decreased or increased compared to usual).
    - Decreased or increased appetite and/or weight.
    - Fatigue/loss of energy.
    - Agitation or slowing of movements.
    - Poor concentration or indecisiveness.
    - Feelings of worthlessness or excessive or inappropriate guilt.
    - Suicidal thoughts or acts.
  - **Duration and associated disability, past and family history of mood disorders and availability of support.**
- The severity of depression is determined by both the number and severity of symptoms, as well as the degree of functional impairment.
  - **Subthreshold depression** is diagnosed if the person has at least two, but fewer than five symptoms of depression.
  - **Mild depression** is diagnosed if the person has few, if any, symptoms in excess of five symptoms and they only result in minor functional impairment.
  - **Moderate depression** is diagnosed if symptoms or functional impairment are between mild and severe.
  - **Severe depression** is diagnosed if the person has most symptoms and they markedly interfere with functioning – they can occur with or without psychotic symptoms.
  - **Persistent subthreshold depressive symptoms (sometimes termed dysthymia) is diagnosed if the person has:**
    - Subthreshold symptoms for more days than not for at least 2 years, which is not the consequence of a partially resolved 'major' depression.
  - **Seasonal affective disorder is diagnosed if the person** has episodes of depression which recur annually at the same time each year with remission in between (usually appearing in winter and remitting in spring).
- **Investigations are not routinely indicated** for people with depression but may be necessary to exclude other causes for symptoms or conditions known to be associated with depression. Basic laboratory tests that may be indicated include:
  - Biochemistry: blood glucose, urea and electrolytes, creatinine, liver function tests, thyroid function tests, calcium levels.
  - Haematology: full blood count and erythrocyte sedimentation rate.

Appendix 2: PHQ-9

The PHQ-9 questionnaire has been validated as a clinical research tool in the detection and assessment of depression (Kroenke 2001 - Journal of General Internal Medicine). Each of the 9 areas listed in the diagnosis is graded by the patient from 0-3, giving a maximum score of 27.

Over the past 2 weeks how often have you been bothered by the following:		
Little interest or pleasure in doing things?	Not at all	0
	Several days	1
	More than half the days	2
	Nearly every day	3
Feeling down, depressed, or hopeless?	Not at all	0
	Several days	1
	More than half the days	2
	Nearly every day	3
Trouble falling or staying asleep, or sleeping too much?	Not at all	0
	Several days	1
	More than half the days	2
	Nearly every day	3
Feeling tired or having little energy?	Not at all	0
	Several days	1
	More than half the days	2
	Nearly every day	3
Poor appetite or overeating?	Not at all	0
	Several days	1
	More than half the days	2
	Nearly every day	3
Feeling bad about yourself — or that you are a failure or have let yourself or your family down?	Not at all	0
	Several days	1
	More than half the days	2
	Nearly every day	3
Trouble concentrating on things, such as reading the newspaper or watching television?	Not at all	0
	Several days	1
	More than half the days	2
	Nearly every day	3
Moving or speaking so slowly that other people could have noticed? Or so fidgety or restless that you have been moving a lot more than usual?	Not at all	0
	Several days	1
	More than half the days	2
	Nearly every day	3
Thoughts that you would be better off dead, or thoughts of hurting yourself in some way?	Not at all	0
	Several days	1
	More than half the days	2
	Nearly every day	3

Scoring: Depression Severity:

0 – 4	None
5 – 9	Mild
10 – 14	Moderate
15 – 19	Moderately severe
20 – 27	Severe

Appendix 3: RCGP RCPsych Suicide Mitigation in Primary Care factsheet June 2012

A factsheet outlining the role of primary care in suicide mitigation: a practical overview of assessing and safely responding to suicidal patients in primary care developed on behalf of the RCGP/RCPsych Primary care Mental Health Forum.

https://www.connectingwithpeople.org/node/41

Appendix 4: Minimum effective doses of antidepressants and licensed starting and maximum doses *(adapted from the Maudsley Prescribing Guideline in Psychiatry, 13th edition, and manufacturer's SPCs)*

Antidepressant	**Minimum effective *adult* dose/day**	**Licensed maximum dose - *adults***	***Older adults* – initial dose and maximum licensed dose**	
SSRIs				
Citalopram	20mg	40mg	10mg	20mg
Escitalopram	10mg	20mg	5mg	10mg
Fluoxetine	20mg	60mg	20mg	40 (– 60mg)
Fluvoxamine	50mg	300mg	50mg	300mg
Paroxetine	20mg	50mg	20mg	40mg
Sertraline	50mg	200mg	25mg	100 - 150mg
Others				
Agomelatine	25mg	50mg	25mg	50mg
Duloxetine	60mg	120mg	30mg	120mg
Mirtazapine	30mg	45mg	15mg	45mg
Moclobemide	300mg	600mg	300mg	600mg
Trazodone	150mg	300mg	100mg	300mg
Venlafaxine	75mg	375mg	37.5mg	150 - 225mg
Vortioxetine	10mg	20mg	5-10mg	20mg
TCAs				
All (except lofepramine)	At least 75-100mg, perhaps 125mg (not completely clear)	See individual SPCs or BNF	See individual SPCs or BNF	
Lofepramine	140mg	210mg	35mg	140 (- 210mg)