PREScribing GUIDELINES FOR THE MANAGEMENT OF DEPRESSION
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Further copies of this document can be found on the Foundation Trust intranet.
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1 Introduction

These guidelines have been developed to provide clinical staff with clear guidance on prescribing for depression to ensure safe effective care of patients in line with current NICE and national good practice guidance and trust formulary. In general, referral to secondary care (the Mental Health Advice and Assessment team) should be made when one or more of the following criteria are met:

1) Psychological therapy (either with IAPT (Improving Access to Psychological Therapies) or elsewhere) is not appropriate or if tried, has not brought about significant improvement.
2) There has been limited or no improvement with adequate doses of two different antidepressants taken consistently for more than six weeks.
3) Lack of improvement is also associated with:
   a) Clinically significant co-morbidity with other mental disorders.
   b) Clinically significant co-morbidity with physical illness which complicates management of disorder.
   c) Complex social care needs which complicate management.
   d) Complex medication management needs, beyond the remit of primary care.
   e) Clinically significant risk factors or safeguarding issues.
4) There is doubt about diagnosis.

If in doubt as to whether it is appropriate to refer, do not hesitate to seek advice from the Mental Health Advice and Assessment teams. In Islington, consider consultation with the Primary Care/IAPT consultant psychiatrist prior to referral to assessment team. If you are unclear about other pathways, please contact your Trust link worker.

2 Aims and objectives

To ensure quality and cost-effective prescribing of medicines and provide optimal treatment of depression.

3 Scope of the policy

This policy relates to prescribing in patients with a diagnosis of depression.

It does not cover prescribing for depression in bi-polar disorder.

It does not cover ECT or psychological therapies, other than to make reference to when they should be considered.
### 4 Key points

#### 4.1 Medicine choice in the treatment of depression.

<table>
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<tr>
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<tr>
<td><strong>First line</strong></td>
<td>Serotonin re-uptake inhibitors.</td>
<td>Formulary options – citalopram, fluoxetine, paroxetine, sertraline.</td>
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<tr>
<td><strong>Second line</strong></td>
<td>Another serotonin reuptake inhibitor or a better tolerated newer generation antidepressant e.g. mirtazapine.</td>
<td>Newer generation antidepressants – mirtazapine, mainserin, venlafaxine.</td>
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<tr>
<td><strong>Third line (3a)</strong></td>
<td>Venlafaxine, a tricyclic antidepressant or moclobemide, phenelzine, vortioxetine</td>
<td>Formulary options (tricyclic antidepressants) – amitriptyline, clomipramine, imipramine, lofepramine. Phenelzine – consultant psychiatrist should be consulted prior to initiation. Vortioxetine is recommended as an option for treating major depressive episodes in adults whose condition has responded inadequately to two antidepressants within the current episode, in particular for patients with treatment emergent sexual dysfunction². A consultant psychiatrist should be consulted prior to initiation.</td>
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<tr>
<td><strong>Third line (3b)</strong></td>
<td>Bupropion (off-label)</td>
<td>Although not included in the current NICE guidance, bupropion may be considered if the other treatment options have failed or are not tolerated. Consultant psychiatrist must be consulted prior to initiation.</td>
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<tr>
<td><strong>Fourth line (4a)</strong></td>
<td>Combination treatments - SSRI plus mirtazapine. Venlafaxine plus mirtazapine.</td>
<td>A consultant psychiatrist should be consulted prior to initiation.</td>
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<tr>
<td><strong>Augmentation treatments – Antidepressant plus lithium. Antidepressant plus an antipsychotic.</strong></td>
<td>A consultant psychiatrist should be consulted prior to initiation. Formulary antipsychotic options – aripiprazole, olanzapine, quetiapine, risperidone. Risperidone is the Trust’s first line antipsychotic medicine. With the exception of quetiapine, atypical antipsychotics are not licensed for the management of depression.</td>
<td></td>
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<tr>
<td><strong>Fourth line (4b)</strong></td>
<td>Combination treatment – a serotonin reuptake inhibitor and bupropion (off-label)</td>
<td>Although not included in the current NICE guidance, bupropion and a serotonin reuptake inhibitor may be considered if the other treatment options have failed or are not tolerated. A consultant psychiatrist must be consulted prior to initiation.</td>
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#### 4.2 There is little evidence to guide prescribing in relation to depression subtypes or personal characteristics. The main issues concern the impact of physical disorders¹.

#### 4.3 Antidepressants should not routinely be used to treat persistent sub-threshold depressive symptoms unless present for at least two years¹,³. Antidepressants should not be used to treat sub-threshold depressive symptoms /mild depression unless other interventions have been unsuccessful¹. Antidepressants should also be considered if
there is a past history of moderate or severe depression\textsuperscript{1}. Antidepressants are a first line treatment for moderate and severe major depression in adults\textsuperscript{3}.

4.4 Antidepressants should not be used routinely for patients with mild depression with chronic physical health problems, unless it complicates the care of the physical health problem\textsuperscript{4}.

4.5 Where an antidepressant is considered appropriate, an SSRI should be considered as first-line pharmacological treatment\textsuperscript{1,3}. If the patient has moderate to severe depression, a combination of an antidepressant with a high-intensity psychological intervention should be given\textsuperscript{1}.

4.6 When depression is accompanied by symptoms of anxiety, the first priority should be to treat the depression. When the person has an anxiety disorder with co-morbid depression or depressive symptoms the NICE guideline for the relevant anxiety disorder should be consulted and treatment of the anxiety disorder should be considered first as effective treatment would often also improve the depressive symptoms\textsuperscript{1}. Refer to the trust anxiety disorder prescribing guidelines on the intranet.

4.7 Antidepressant options should be discussed with the patient including anticipated adverse events, discontinuation symptoms and potential interactions with medicines or physical health problems. See section 6 to 17. Also the patient's perception of the efficacy and tolerability of any previous antidepressants taken should be considered\textsuperscript{1}.

4.8 Patients should be advised of:

- the nature of the illness\textsuperscript{3}.
- gradual development of the full antidepressant effect\textsuperscript{1}.
- the importance of taking the antidepressant as prescribed and the need to continue beyond the depressive episode\textsuperscript{1,5}.
- the duration of treatment\textsuperscript{6}.
- the potential side effects and interactions with concomitant medicines or physical health conditions\textsuperscript{1}.
- symptoms (usually mild and self-limiting over one week, but can be severe particularly if the medicine is stopped abruptly). Although antidepressants are not associated with dependence, discontinuation/withdrawal symptoms may occur on stopping or missing doses or occasionally on reducing doses (especially medicines with shorter half-lives e.g. paroxetine and venlafaxine)\textsuperscript{1}.
- the most commonly experienced discontinuation/withdrawal symptoms are dizziness, numbness and tingling, gastrointestinal, headache, sweating, anxiety and sleep disturbances\textsuperscript{1}.
- the need to seek medical advice if they experience discontinuation/withdrawal symptoms\textsuperscript{1}.

Appropriate leaflets should be provided from the Choice and Medication website:-
http://www.choiceandmedication.org/candi/
4.9 The patient’s perception of the efficacy and tolerability of previous antidepressants prescribed should be considered.

4.10 Patients under 30 years should be warned that these medicines are associated with an increased risk of suicidal thinking and self-harm in a minority of patients.

4.11 When prescribing for older people, prescribe an age appropriate dose taking into account the effect of physical health and concomitant medication. Side effects should be carefully monitored.

4.12 Patients should be advised if the medicines are prescribed off-label. They should be offered patient information leaflets from the ‘Choice and Medication’ link on the trust intranet.

4.13 Citalopram and to a lesser extent sertraline have fewer propensities for medicine interactions. Fluoxetine, fluvoxamine and paroxetine are associated with a higher propensity for medicine interactions than other SSRIs.

4.14 Citalopram is associated with a dose dependent risk of QT prolongation. The maximum dose in adults is 40mg and in older adults it is 20mg per day. See section 11.

4.15 Paroxetine is associated with a higher incidence of discontinuation symptoms than other SSRIs. Venlafaxine is also associated with a higher incidence of discontinuation symptoms.

4.16 When prescribing medicines other than serotonin reuptake inhibitors, the increased likelihood of the person stopping treatment because of side effects (and the consequent need to increase the dose gradually) with venlafaxine and tricyclic antidepressants should be considered.

4.17 The following should be considered when patients are initiated on venlafaxine:

- Likelihood of stopping treatment because of its side effect profile.
- Venlafaxine is associated with a greater risk of death compared with other routinely used antidepressants.
- Higher doses of venlafaxine are associated with exacerbation of cardiac arrhythmias and hypertension. Patients’ blood pressure should be monitored at higher doses. Also see section 5.27.
4.18 Patients who have been prescribed bupropion long-term for the management of depression (e.g. patients from abroad where bupropion is licensed for depression), may have treatment continued. Patients newly prescribed bupropion in the private sector should be reviewed and an alternative considered if appropriate (i.e. in accordance with NICE guidance). Bupropion alone may be considered if patients have not benefited from antidepressants recommended in the NICE guidelines and monotherapy is preferable. Alternatively it may be considered as an adjunctive treatment for the management of treatment resistant depression if the patient has not benefited from other options advised by NICE (see table 1). There must be clear communication with the GP regarding the treatment plan and off-label use.

4.19 Toxicity in overdose should be taken into account when selecting an antidepressant for patients at significant risk of suicide. Venlafaxine is associated with a greater risk of death from overdose. Tricyclic antidepressants (except for lofepramine) are associated with the risk in overdose.

4.20 Tricyclic antidepressants have the potential to cause postural hypotension and arrhythmias. Dosulepin should not be prescribed.

4.21 Older tricyclic antidepressants should generally be reserved for situations when first-line medicine treatment, have failed. See table 1.

4.22 Non-reversible monoamine oxidase inhibitors such as phenelzine should normally only be initiated by a specialist mental health professional.

4.23 Advise people taking a monoamine oxidase inhibitor of the dietary and pharmacological restrictions concerning the use of these drugs as set out in the British National Formulary.

**Patient counselling**

Patients should be advised to eat only fresh foods and avoid food that is suspected of being stale or ‘going off’. This is especially important with meat, fish, poultry or offal; game should be avoided. The danger of interaction persists for up to 2 weeks after treatment with MAOIs is discontinued. Patients should also avoid alcoholic drinks or de-alcoholised (low alcohol) drinks.
4.24 Haematological monitoring is required for elderly patients prescribed mianserin\(^1\).

4.25 Agomelatine should not be started if serum transaminases exceed three times the upper limit of the reference range. Liver function should be tested before treatment and after three, six, twelve and twenty four weeks of treatment, and then regularly thereafter when clinically indicated. The monitoring schedule should be restarted when the dose is increased. Agomelatine should be discontinued if the serum transaminases exceed three times the upper limit of the reference range or symptoms of liver disorder. Patients should be told how to recognise signs of liver disorder and advised to seek immediate medical attention if symptoms such as dark urine, light coloured stool, jaundice, bruising, fatigue, abdominal pain or pruritus develop\(^9\). Agomelatine should be requested via the non-formulary route.

4.26 There is no evidence supporting the use of specific antidepressants for patients with particular chronic physical health problems\(^4\), but some recommendations are made in later sections.

4.27 It is appropriate to consider using the lowest effective dose in pregnancy and breastfeeding. Treatments should not be stopped abruptly.

4.28 A partial treatment response may take up to four weeks with a full response taking a further four weeks\(^1\).

4.29 Refer to the Trust guidelines for the management of insomnia if patients have problems sleeping.

4.30 The management of bipolar depression is outside the scope of this guideline.

4.31 The use of electroconvulsive therapy is outside the scope of this guidance.

4.32 Patients with depression who are considered to be at significant risk of relapse (including those who have relapsed despite antidepressant treatment or who are unable or choose not to continue antidepressant treatment) or who have residual symptoms, should be offered a psychological intervention\(^1\).

4.33 Psychological interventions are outside the scope of this guidance.

4.34 GPs in Islington can obtain further prescribing advice from Consultant Psychiatrist Islington iCope/Primary care (see appendix 3). There is not an equivalent service in Camden.

5 Treatment of Depression
   i. Prior to initiation of treatment

5.1 Before prescribing, the following factors should be considered:-

- Associated psychiatric disorder that may specifically respond to a particular antidepressant e.g. obsessive compulsive disorder and serotonin reuptake inhibitors\(^3, 5\) and general medical problems\(^5\) that make the antidepressant less well tolerated\(^5\).
- Patient preference\(^3\).
- Previous treatment response to a particular antidepressant\(^3\).
- Tolerance and adverse effects of a previously prescribed medicine\(^3\).
- Tendency to produce a withdrawal syndrome especially with paroxetine and venlafaxine
- Side effect profile and potential for medicine interactions e.g. serotonin reuptake inhibitors and tramadol sedation, sexual side effects, weight gain
- Tolerability and adverse effects to previous treatment
- If at a later stage choosing between a tricyclic antidepressant or a monoamine oxidase inhibitor, a family history of differential antidepressant response
- If at a later stage of treatment, the presence of atypical features (responds less well to imipramine than phenelzine).
- The risk of suicide and likelihood of toxicity in overdose if an antidepressant is prescribed (especially with venlafaxine or tricyclic antidepressants) or other concurrent medication. If necessary limit the amount of medicine (s) available.
- The person's prior experience of treatment with individual medicines especially previous response, adherence, effectiveness, side effects, experience of withdrawal syndrome and the person's preference.
- Consider increased potential risk of suicidality in young adults less than thirty years of age when prescribing SSRIs. These patients should be seen within one week of prescribing and then frequently thereafter until the risk is no longer considered clinically important. Other patients can be seen after two weeks, then every two to four weeks for the first three months, then at longer intervals if the response is good.

5.2 If side effects develop, provide appropriate information and consider:

- monitoring side effects if mild and acceptable to the person.
- stopping the antidepressant or changing the antidepressant to a different one if the person prefers.
- if anxiety, agitation and/or insomnia is present, short-term (two weeks) concomitant treatment with a benzodiazepine (except in people with chronic symptoms of anxiety). This should usually be for no longer than two weeks in order to prevent the development of dependence.

5.3 An initial response to an antidepressant may begin to occur two weeks after commencing treatment.

5.4 In adults, if there is symptomatic improvement by four weeks, continue for another two to four weeks. Consider switching to another antidepressant if:

- the response is inadequate or
- there are side effects
- the person prefers to change treatment.

5.5 Some antidepressants have modest evidence for a dose-response e.g. venlafaxine and tricyclic antidepressants.

5.6 When prescribing for older people, prescribe an age appropriate dose taking into account the effect of physical health and concomitant medication.

5.7 In older adults, treatment should be continued for six weeks before considering a switch. If there is a symptomatic improvement after six weeks, they may require a longer period to further respond thereafter.

5.8 When prescribing an older tricyclic antidepressant or an antidepressant requiring dose titration, the dose should be increased every three to seven days to allow adjustment.
to side effects The target dose of a tricyclic antidepressant as an imipramine dose equivalence of equal or more than 125mg per day if tolerated3.

5.9 If a patient has responded to a lower than a target dose of an antidepressant, the dose should still be increased to one of established efficacy if possible to reduce the the likelihood of relapse in continuation treatment. Where this is not possible, the medicine should be continued at the same dose and the patient monitored for relapse3.

5.10 Patients who are started on low dose tricyclic antidepressants and who have a clear response can be maintained on that dose with careful monitoring1.

ii. Inadequate response

5.11 If response is absent or minimal after three to four weeks of treatment with a therapeutic dose of an antidepressant, check adherence to the prescribed dose and side effects from initial treatment. Increase the frequency of appointments using outcome monitoring with a validated outcome measure. Consider weekly face to face contact or telephone contact1.

5.12 Be aware that using a single antidepressant rather than combination medication or augmentation is usually associated with a lower side effect burden1.

5.13 Also consider:

- Increasing the dose within the specification of product characteristics if there are no significant side effects1. Increase the dose to the recommended therapeutic dose if only a low or a marginal dose has been achieved3.
- Switching to another antidepressant if there are side effects or if the person prefers this option1

5.14 If there is minimal improvement, then a dose increase, a switch or combination/augmentation therapy should be considered. If patients have failed a number of treatments, longer trials should be considered before changing treatment3.

5.15 Consider reintroducing previous treatments that have been inadequately delivered or adhered to, including increasing the dose1.

5.16 Review diagnosis including the possibility of other psychiatric or medical diagnoses3.

5.17 The combination of antidepressant medication and cognitive behavioural therapy should be considered.1

iii. Switching

5.18 Switching antidepressants should be considered especially if:-

- there are troublesome or dose-limiting side effects and/or
- there has been no improvement3.

5.19 A switch should be made within the class e.g. from serotonin reuptake inhibitor to another or to another class (see table 1)3. When switching to another antidepressant, consider switching to initially a different SSRI or a better tolerated newer generation antidepressant e.g. mirtazapine. Subsequently an antidepressant of a different pharmacological class could then be considered e.g. venlafaxine, a tricyclic
antidepressant or a monoamine oxidase inhibitor (see table 1). Dosulepin should not be initiated due to its increased cardiac risk and toxicity in overdose.\(^1\)

5.20 An antidepressant of a different class should be considered after more than one failure with a specific class e.g. venlafaxine should be considered after more than one failure with a serotonin reuptake inhibitor (see table 1).\(^3\)

5.21 All antidepressants have the potential to cause withdrawal phenomena. When taken continuously for six weeks or longer, antidepressants should not be stopped abruptly unless a serious adverse event has occurred.\(^6\)

5.22 Switching between antidepressants should be done cautiously. Discontinuation syndrome, pharmacokinetic (e.g. elevation of tricyclic plasma levels by serotonin reuptake inhibitors) or pharmacodynamics interactions (e.g. serotonin syndrome) may be encountered during switching.\(^6\)

5.23 The speed of the cross-tapering should be judged by assessing patients' tolerability. There are no set guidelines on how to do cross taper it is based on pharmacological principles. It should be done cautiously and depends on the patient, the antidepressants used and the doses. See appendix 2 or a current copy of the Maudsley prescribing guidelines.

5.24 In some cases cross-tapering may not be necessary e.g. when swapping from one serotonin reuptake inhibitor to another.\(^6\)

5.25 When switching, particular caution should be taken when switching from:

- flouxetine to other antidepressants due to its long half-life (one week).\(^1\)
- flouxetine or paroxetine to a tricyclic antidepressant because they both inhibit the metabolism of tricyclic antidepressants. A lower starting dose of a tricyclic antidepressant will be required particularly if switching from flouxetine because of its long half-life.\(^1\)

5.26 a non-reversible monoamine oxidase inhibitor. A two week washout period is required (other antidepressants should not be prescribed routinely during this period) because of the dangers of the dietary and medicines interactions and the risk of interaction persists for up to two weeks after treatment with a monoamine oxidase is discontinued. See appendix 2.

When switching to a new serotonergic antidepressant or a monoamine oxidase inhibitor, caution should be exercised because of the risk of serotonin syndrome\(^1\) (see table 2). Also see the 'Choice and Medication' link for a leaflet - http://www.choiceandmedication.org/candi/pdf/handyfactsheetserotoninsyndrome.pdf

5.27 The following should be considered when patients are initiated on venlafaxine:

- Likelihood of stopping treatment because of its side effect profile.\(^1\)
- Venlafaxine is associated with a greater risk of death compared with other routinely used antidepressants.\(^1\)
- Higher doses of venlafaxine are associated with exacerbation of cardiac arrhythmias and hypertension. Patients' blood pressure should be monitored at higher doses.\(^1\)
- Doses above 300mg per day should be prescribed under specialist supervision.\(^10\)
- Venlafaxine is contraindicated in patients with an identified high risk of serious cardiac ventricular arrhythmias or in patients with uncontrolled hypertension\(^9\).
- Venlafaxine has a higher propensity for discontinuation/withdrawal symptoms if stopped abruptly\(^1\).
- Avoid co-administration of erythromycin (potent CYP3A4) unless strictly indicated because the possibility of clinically important interactions in patients with a ‘poor metaboliser' phenotype\(^10\).

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<thead>
<tr>
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<tr>
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<td></td>
<td>Diaphoresis</td>
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<td>Tremor</td>
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<td>Shivering</td>
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<td>Myoclonus</td>
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<td>Confusion</td>
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<td></td>
<td>Convulsions</td>
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<td></td>
<td>Death</td>
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</tbody>
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### Table 2: Symptoms of serotonin syndrome\(^b\)

#### iv. Combining antidepressants

5.28 Combination therapy is when two antidepressants are used together\(^1\).

5.29 Combination therapy should be considered if
- there is partial/insufficient response on the current antidepressant and
- there is good tolerability of the current antidepressant or
- switching the antidepressant has been unsuccessful\(^3\).

5.30 If a person is informed about and prepared to tolerate the increased side effect burden, consider combining antidepressants\(^1\).

5.31 When combining antidepressants, select antidepressants known to be safe together and be aware of the increased side effect burden (see table 1)\(^1\).

5.32 If an unusual combination is to be used, consider obtaining a second opinion\(^1\). Also refer to the unlicensed medicines and unlicensed use of licensed medicines (off-label) policy.

5.33 The rationale for the combination should be discussed with the patient and monitor for adverse effects. The rationale should also be documented\(^1\). Also refer to the unlicensed medicines and unlicensed use of licensed medicines (off-label) policy.

5.34 When combining antidepressants, the patient needs to be monitored even more carefully for side effects\(^1\) and for signs and symptoms of serotonin syndrome (see table 2).

#### v. Augmenting antidepressants with non-antidepressants

5.35 Augmentation is when an antidepressant is used with a non-antidepressant\(^1\).

5.36 Augmentation therapy should be considered if
- there is partial/insufficient response on the current antidepressant and
- there is good tolerability of the current antidepressant or
• switching the antidepressant has been unsuccessful³.

5.37 If a person is informed about and prepared to tolerate the increased side effect burden, consider augmenting the antidepressant.¹

5.38 When using augmentation therapy, select medicines known to be safe together and be aware of the increased side effect burden (see table 1)¹.

5.39 Augmentation of an antidepressant with a non-antidepressant medicine includes the following options – lithium, risperidone, aripiprazole, olanzapine or quetiapine¹.

5.40 If an unusual combination is to be used, consider obtaining a second opinion¹. Also refer to the unlicensed medicines and unlicensed use of licensed medicines (off-label) policy.

5.41 The rationale for the combination should be discussed with the patient and monitor for adverse effects. The rationale should also be documented¹. Also refer to the unlicensed medicines and unlicensed use of licensed medicines (off-label) policy.

5.42 When using augmentation therapy, the patient needs to be monitored even more carefully for side effects¹.

5.43 When prescribing lithium:

• Aim for a plasma level of 0.4 with an optimal range 0.6-0.75mmol/l. Maximum serum level: 1.0mmol/l⁶.
• Monitor renal and thyroid function before treatment and every six months. If there is evidence of renal impairment, relevant physical illness, elderly, interacting medicines, monitoring should occur more often. Weight should also be monitored¹,⁶.
• Consider ECG monitoring in patients at high risk of cardiovascular disease⁶.
• Monitor serum lithium levels one week after initiation and each dose change until stable and every three months thereafter¹.
• Continue it in patients who needed lithium augmentation of antidepressants in acute treatment¹.
• Adjunctive treatment with lithium reduces the risk of relapse or suicide³,¹¹. If discontinuing one medicine, the preference is lithium as it is not advisable to prescribe lithium alone for depression¹,³.
• Lithium should be slowly reduced over at least one month. Incremental reduction in plasma levels of greater than 0.2mmol/l should be avoided⁶.
• The patient must be given a lithium patient information booklet: http://www.nrls.npsa.nhs.uk/EasySiteWeb/getresource.axd?AssetID=65431
• http://www.choiceandmedication.org/candi/pdf/pilllithium.pdf
5.44 When prescribing an antipsychotic, monitor weight, lipid and glucose levels and for side effects e.g. extrapyramidal side effects and prolactin related side effects with risperidone.¹

5.45 For patients with depression with psychotic symptoms, augmentation of the antidepressant with an antipsychotic (e.g. olanzapine or quetiapine⁶) should be considered. The optimum dose and duration of treatment is unknown.¹ Tricyclic antidepressants are probably the medicines of first choice in psychotic depression⁶. Initial augmentation is preferable to an antidepressant alone or an antipsychotic alone³.

5.46 The combination of an antidepressant with a benzodiazepine for more than two weeks should not be used routinely as there is a risk of dependence¹.

Vi Combined psychological and medicine treatment

5.47 If a patient has not responded to either pharmacological or psychological interventions a combination of medication with CBT should be considered¹.

Vii Electroconvulsive therapy

5.48 Electroconvulsive therapy should be considered for acute treatment of severe depression (including psychotic depression⁶) that is life-threatening and when a rapid response is required or when other treatments have failed¹.

5.49 ECT should not routinely be used for people with moderate depression, unless they have not responded to multiple medication treatments and psychological treatments¹.
Complex and severe depression

5.50 Patients would include patients at significant risk of self-harm, have psychotic symptoms, require complex multiprofessional care, or where an expert opinion on treatment and management is needed.

5.51 For a person whose depression has failed to respond to various strategies for augmentation and combination treatments, consider a referral to a specialist service.

5.52 After thoroughly reviewing previous treatments for depression, the re-introduction of previous treatments that have been inadequately delivered or adhered to should be considered.

5.53 Other treatment options not listed in table 1 e.g. adjunctive treatment with tri-iodothyronine, buspirone and lamotrigine are non-formulary and should be requested via the non-formulary route.

Continuation of treatment

5.54 Patients who have benefited from taking an antidepressant should be supported in taking it for at least six months. A discussion with the patient should explain that:

- this greatly reduces the risk of relapse;
- antidepressants are not associated with addiction.

5.55 The person should be reviewed for the need for continued antidepressant treatment beyond six months after remission. The following should be taken into account:

- number of previous episodes,
- consequences of relapse,
- presence of residual symptoms, concurrent physical health problems and psychosocial difficulties.

5.56 Following remission, the antidepressant treatment should be continued at the same dose for at least six months.

5.57 Following remission, older adult patients should continue treatment for at least twelve months.

5.58 Patients with recurrent depression should receive maintenance treatment for at least two years.

5.59 Following 2 years of maintenance antidepressant treatment, patients should be reassessed according to age and co-morbidity and other risk factors.

Relapse prevention

5.60 For patients with depression who are at significant risk of relapse or have a history of recurrent depression a discussion should take place on treatments to reduce the risk of recurrence, including continuing medication, augmentation of medication or CBT. Treatment should be influenced by:

- previous treatment history including the consequences of a relapse, residual symptoms, response of previous treatment and any discontinuation symptoms.
- the patient’s preference.
• the adequacy of treatment including dose and adherence³.
• a review of the diagnosis including the possibility of additional psychiatric or medical diagnoses³.

5.61 Relapses may be self-limiting and therefore caution should be exercised about frequent or too-early treatment changes³.

5.62 Medication responsive patients should have their medication continued at the acute treatment dose after remission with the duration determined by risk of relapse³.

5.63 In patients at lower risk of relapse e.g. first episode patients without other risk factors, the duration should be at least six to nine months after full remission³.

5.64 If a person is at risk of relapse, treatment should be continued for at least two years at the effective dose¹.

5.65 In patients with more than five lifetime episodes and/or two episodes in the last few years, at least two years should be advised and for most, long-term treatment should be considered⁰.

5.66 There is evidence that continued antidepressant treatment in older people halves relapse rates³.

5.67 The level of medication should be maintained at which acute treatment was effective (unless there is a good reason to reduce the dose such as unacceptable adverse effects) if:-
• they have had two or more episodes of depression in the recent past during which they experienced significant functional impairment.
• they have other risk factors for relapse such as residual symptoms, multiple previous episodes or a history of severe or prolonged episodes or of an inadequate response.
• the consequences of relapse are likely to be severe (for example suicide symptoms, loss of functioning severe life disruption and inability to work¹).

5.68 When deciding whether to continue maintenance treatment beyond two years, a re-evaluation of the patient taking into account age, co-morbid conditions and other risk factors¹.

5.69 Patient with depression on long-term maintenance treatment should be regularly re-evaluated with frequency of contact determined by:-
• co-morbid conditions¹.
• risk factors for relapse¹
• severity and frequency of episodes of depression¹.

5.70 If a relapse occurred, treatment options are:-
• If an antidepressant has been stopped, re-initiation of an antidepressant at an adequate dose⁹.
• If the dose has been lowered, re-establish the previous dose³.
• If the patient is on an adequate dose (with a recent onset relapse), support and monitoring without dose changes should be considered³.
• Increasing the dose subject to the following: there are minimal side effects and/or there has been some improvement on the antidepressant and/or the current antidepressant has a possible dose response e.g. venlafaxine and tricyclic antidepressants³.
• Other options are switching the antidepressant, combination or augmentation therapy\textsuperscript{3}.
5.71 If a person has had a good response to an antidepressant and an augmenting agent he/she should remain on the combination after remission if side effects are acceptable. If one medicine is stopped, it should usually be the augmenting agent. Lithium should not be used as a sole agent to prevent recurrence of depression.

5.72 If a person’s depression has responded to a course of ECT, antidepressant medication should be started or continued to prevent relapse. Consider lithium augmentation of antidepressants.

5.73 Patients who are considered to be at significant risk of relapse (including those who have relapsed despite antidepressant treatment or who are unable or choose not to continue antidepressant treatment) or who have residual symptoms should be offered psychological interventions. Psychological interventions are outside the scope of this guidance.

XI Stopping and reducing antidepressants

5.74 When stopping antidepressant treatment after a period of prophylaxis, the timing should be matched to both risk and consequences of relapse and the patient should be warned that the highest risk is in the six months after stopping it.

5.75 The clinical situation should be taken into account when determining the rate of taper e.g. serious adverse reactions may warrant rapid discontinuation. Antidepressants should normally be stopped over a four week period, but this may be longer if paroxetine or venlafaxine was prescribed. Fluoxetine does not require a tapering off period due to its long half-life. Recommendations are based on pharmacological principles and details depend on the patient, the antidepressant used, dose and the duration of treatment. A longer period may be required for patients receiving monoamine oxidase inhibitors especially tranylcypromine. Tranylcypromine is partly metabolised to amphetamine and is therefore associated with a true withdrawal syndrome. A period of some months may be appropriate for planned treatment withdrawal after long-term prophylaxis.

5.76 The specification of product characteristics for vortioxetine states patients can stop treatment abruptly without the need for a gradual reduction in dose.

5.77 People should be advised discontinuation symptoms may occur on stopping treatment, missing doses or reducing doses. Symptoms are usually mild and self-limiting over one week but can be severe particularly if the medicine is stopped abruptly. Patients should be warned that a discontinuation reaction may occur if treatment is abruptly stopped after more than a few weeks of treatment (the risk is increased after eight weeks or longer). In addition, patients should be advised antidepressants are not addictive. Paroxetine and venlafaxine are more likely to cause the symptoms.

5.78 The onset of symptoms is usually within five days of stopping treatment or occasionally after tapering or missing doses.

5.79 Symptoms vary depending on the type of antidepressant (see a current copy of the Maudsley prescribing guidelines) but may include flu-like symptoms, irritability, paraesthesia, increased dreaming, insomnia and rarely movement disorders or mania.

5.80 If discontinuation symptoms occur, monitor symptoms and reassure the person if the symptoms are mild. If severe, consider reintroducing the antidepressant or introduce an antidepressant with a longer half-life from the same class. Then reduce the dose.
gradually while monitoring symptoms\(^1\). For example for serotonin reuptake inhibitor or a serotonin-noradrenaline reuptake inhibitor, consider switching to fluoxetine which can then be stopped after discontinuation symptoms have fully subsided\(^3,6\).

**5.81** If a patient switches to a hypomanic state, consideration of stopping the antidepressant should be made\(^{15}\). This can be done abruptly or gradually depending on the patient current clinical need, previous experience of discontinuation symptoms and risk of discontinuation symptoms of the antidepressant in question. An intolerable adverse reaction may necessitate an abrupt discontinuation\(^3\). Refer to the trust guidelines for the management of bipolar affective disorder.

**5.82** The patient should be advised that he/she should seek advice from their practitioner if they experience significant discontinuation symptoms. If discontinuation symptoms occur:

- symptoms should be monitored and the patient reassured if the symptoms are mild.
- consider the reintroduction of the original antidepressant at the dose that was effective (or another antidepressant with longer half-life from the same class) if symptoms are severe, and reduce the dose gradually while monitoring symptoms\(^1\).
5.83 A general leaflet on ‘Coming off medicines’ is available on the Choice and Medication link on the intranet: http://www.choiceandmedication.org/candi/pdf/handyfactsheetstoppingmedicines.pdf

6 Older adults

6.1 There is no ideal antidepressant as all are associated with problems. Serotonin reuptake inhibitors are better tolerated than tricyclic antidepressants, but they do have an increased risk of bleeds particularly those with a history of bleeds or prescribed a non-steroidal medicine, aspirin, steroids or warfarin. If a non-steroidal medicine or aspirin is prescribed, a concurrent prescription for a gastroprotective agent should be considered\(^1\). The risk of haemorrhagic stroke may also be increased. Hyponatraemia, postural hypotension and falls (the consequence of which may be increased by serotonin reuptake inhibitor induced osteopenia) are also a risk\(^6\).

6.2 An age appropriate dose should be prescribed taking into account general physical health and effect of concomitant medication on pharmacodynamics and pharmacokinetics\(^1\).

6.3 In older people, response to antidepressants may take longer\(^3\). A minimum of six weeks treatment should be given before considering the treatment to be ineffective\(^6\), but it may be possible to identify non-responders as early as four weeks\(^6\).

6.4 Antidepressants should be initiated at lower doses than used for younger adults\(^11\).

6.5 The evidence base for switching antidepressants or augmenting antidepressants is smaller than for younger patients. Overall 50% of patients respond. The best evidence is for lithium augmentation\(^3\).

6.6 There is a poorer response and a high risk of relapse in elderly\(^8\) with co-morbid medical illness\(^3\).

6.7 There is evidence that continued antidepressant treatment in older people halves relapse rates\(^3\).

6.8 The average older adult is more likely to be taking concurrent medicines\(^1\) leading to a potential for medicines-medicine and medicines-disease interactions. Refer to the summary of product characteristics or the British National Formulary for further information\(^9,14\).

6.9 Hyponatraemia is common in the elderly\(^11\) and thus careful monitoring is advised in this patient group as older age is a risk factor (see section10\(^6\)).

6.10 The review of epidemiological studies, mainly in patient age 50 years or older shows an increased risk of bone fractures in patients receiving serotonin reuptake inhibitors and tricyclic antidepressants. The mechanism leading to this increased risk is unclear\(^15\).

6.11 Depression in older adults with dementia should be prescribed according to the same principles as older adults, after a careful risk assessment. Antidepressants with anticholinergic side effects should be avoided where possible as they adversely affect cognition\(^16\).
7 Post stroke depression

7.1 Antidepressants recommended in post-stroke depression are serotonin re-uptake inhibitors and nortriptyline. Note nortriptyline should be requested via the non-formulary route. However caution is indicated if the index stroke was known to be haemorrhagic because serotonin reuptake inhibitors increase the risk of haemorrhagic stroke (absolute risk is low) when combined with warfarin or other antiplatelet medicines. If the patient is taking warfarin, citalopram should be suggested as it has the lowest interaction potential. If the serotonin reuptake inhibitor is given to an anti-coagulated or aspirin treated patient, a prescription for a proton pump inhibitor should be considered.

8 Side effects of antidepressants

8.1 If possible, side effects likely to be transient should be discussed and if necessary a dose reduction and re-titration.

8.2 If persistent, severe or distressing side effects options are:
- Dose reduction and re-titration if possible.
- Switching to an antidepressant with a lower propensity to cause side effects.
- Non-medicine management of the side effect e.g. diet and exercise.
- Symptomatic treatment with a second medicine e.g. benzodiazepines for agitation or a hypnotic for insomnia.
- Specialist referral e.g. for sexual dysfunction.

9 Suicidality

Antidepressant treatment has been associated with an increased risk of suicidal thoughts and acts particularly in young adults. All antidepressants have been implicated including those marketed for an indication other than depression (e.g. atomoxetine). It should be noted that:
- although the relative risk may be elevated above placebo rates in some patient groups, the absolute risk remains very small.
- the most effective way to prevent suicidal thoughts and acts is to treat depression.
- antidepressant medicines are most effective treatment currently available.

For the most part, suicidality is greatly reduced by the use of antidepressants. Those who experience treatment emergent or worsening suicidal ideation with one antidepressant may be more likely to have a similar experience with subsequent treatments. Toxicity in overdose varies both between and within groups of antidepressants. For further information, see the section on ‘Psychotropics in overdose’ in the Maudsley prescribing guidelines.
10 Antidepressant-induced hyponatraemia

10.1 Consider hyponatraemia with antidepressants especially serotonergic medicines. The onset is usually within thirty days of starting treatment. Symptoms include headache, dizziness, nausea, vomiting, confusion, malaise, restlessness, lethargy, cramps, disorientation and seizures. Risk factors include history of hyponatraemia, low body weight, extreme old age (>80 years) or female patients, low baseline sodium concentration, reduced renal function, warm weather, medical co-morbidity and some medicines

10.2 Medical co-morbidities that are risk factors are hypothyroidism, diabetes, chronic obstructive pulmonary disease, hypertension, head injury, congestive heart failure, cerebrovascular disease and various cancers.

10.3 Medicines which may be a risk factor for developing hyponatraemia include carbamazepine, antipsychotics, diuretics, non-steroidal medicines, tramadol, omeprazole and trimethoprim, calcium antagonists and angiotensin converting enzyme inhibitors.

10.4 The normal range for serum sodium is 135 – 145 mmol/l (Whittington ICE).

10.5 If the serum sodium is >125 mmol/l, monitor sodium until normal. Symptoms are listed above. Consider withdrawing the antidepressant. If the serum sodium is < 125 mmol/l, refer to specialist medical care as there is an increased risk of seizures, coma and respiratory arrest. The antidepressant should be discontinued immediately. Discontinuation symptoms may complicate the clinical picture.

10.6 When restarting an antidepressant, prescribe an antidepressant from a different class either a noradrenergic medicine such as lofepramine, mirtazapine, reversible monoamine oxidase inhibitor (moclobemide). Nortriptyline or agomelatine are other options, but should be requested via the non-formulary route.

10.7 Electroconvulsive therapy could be considered as an option.

10.8 See the Choice and Medication link for leaflet on hyponatraemia: http://www.choiceandmedication.org/candi/pdf/handyfactsheethyponatraemia.pdf

11 Cardiovascular disease

11.1 Non-tricyclic antidepressants generally have a low risk of inducing arrhythmias. However antidepressants should be used with caution in patients with risk factors for QT prolongation. Hypokalaemia and hypomagnesaemia should be corrected prior to treatment. For high risk patients (e.g. congenital long QT syndrome, bradycardia, ischaemic heart disease, myocarditis, myocardial infarction, left ventricular hypertrophy, a genetic predisposition, pre-existing QT prolongation, old age, female gender, hypokalaemia, hypomagnesaemia, hypocalcaemia, extreme physical exertion, stress or shock, anorexia nervosa and medicine interactions), ECG monitoring should be performed. Consideration should be given to stopping the antidepressant or reducing the dose of the QT interval is >500ms or increases by 60ms. A QT > 500ms or an increase of > 60ms during treatment confers a high risk of Torsades de Pointes.

11.2 QT prolongation appears to be a class effect for all selective serotonin reuptake inhibitors and tricyclic antidepressants and also occurs with venlafaxine. There are no high quality data comparing the risk of QT prolongation between different
antidepressants (other than citalopram and escitalopram). If QT prolongation or symptomatic arrhythmia occurs during antidepressant treatment, the antidepressant should be stopped or the dose reduced and specialist advice sought.\(^{17}\)

11.3 Citalopram is associated with a dose-dependent risk of QT prolongation\(^{5,18}\). The maximum dose in adults is 40mg and in older adults it is 20mg per day.\(^{5,18}\) Citalopram is contraindicated with other medicines that prolong QTc, patients with known QT prolongation or congenital long QT syndrome.\(^{7,9,18}\) As antipsychotics can prolong the QTc interval\(^{6}\) see the table in the Maudsley Prescribing guidelines for the propensity for antipsychotics to prolong the QTc interval. Careful consideration of the risk/benefit must be given before any decision to prescribe combination therapy with antipsychotics or if patients are prescribed other concurrent medicines that affect QTc.

11.4 See the trust antipsychotic guidelines for the table on the effects of antipsychotic medicines on the QTc interval.

11.5 Caution is advised in patients with significant bradycardia or in patients with recent acute myocardial infarction or uncompensated heart failure.\(^{18}\) Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk of malignant arrhythmias and should be corrected before treatment with citalopram is started. A baseline ECG is advised prior to initiating citalopram in patients with stable cardiac disease.\(^{7}\)

11.6 Sertraline is the treatment of choice for patients with a recent myocardial infarction\(^{6}\) or unstable angina\(^{9}\). Other SSRIs\(^{5}\) and mirtazapine\(^{6}\) are likely to be safe.

11.7 Tricyclic antidepressants should be avoided in patients at risk of serious arrhythmia due to their arrhythmogenic potential, which is dose-related. If the use of tricyclic antidepressants cannot be avoided, the baseline blood pressure should be checked and an ECG should be performed at baseline one week after each increase in dose and periodically throughout treatment. The frequency is determined by the stability of the cardiac disorder, the tricyclic antidepressant and the dose used. Advice should be sought from a cardiologist. Lofepramine seems to lack the arrhythmogenicity of other tricyclic antidepressants.\(^{6}\)

11.8 Bupropion, escitalopram (non-formulary), citalopram, moclobemide, lofepramine and venlafaxine should be used with caution or avoided in those at risk of serious arrhythmia (those with heart failure, left ventricular hypertrophy, previous arrhythmia or an MI). An ECG should be performed at baseline and one week after every increase in dose if any of these medicines are used at risk patients.\(^{6}\)

11.9 The arrhythmogenic potential of tricyclic antidepressants and other antidepressants is dose related. ECG monitoring should be considered for all patients:
  - prescribed doses towards the top of the licensed range.
  - prescribed other medicines (e.g. fluoxetine and diuretics) that through medicine interactions may add to the risk posed by the tricyclic antidepressant.\(^{6}\)
11.10 In acute coronary syndrome, medicines which do not increase the risk of subsequent cardiac events should be considered. The best evidence is for serotonin reuptake inhibitors, mirtazapine and bupropion.

11.11 If possible, tricyclic antidepressants should be avoided in cardiac failure and cardiovascular disease.

12 Co-morbid Diabetes

12.1 Fluoxetine has been associated with improvements in HbA1c levels and reduced insulin requirements. Sertraline may also reduce HbA1c. However evidence is accumulating that long-term use of serotonin reuptake inhibitors may increase the risk of diabetes to a modest extent.

12.2 Serotonin-noradrenaline reuptake inhibitors do not appear to disrupt glycaemic control, but there is limited data with venlafaxine.

12.3 Little is known about the effect of mirtazapine.

12.4 Tricyclic antidepressants are associated with increased appetite, weight gain and hyperglycaemia. Long-term use of tricyclic antidepressants seems to increase the risk of diabetes.

12.5 Irreversible monoamine oxidase inhibitors have a tendency to cause extreme hypoglycaemia episodes and weight gain. Moclobemide has no known effects.

13 Weight gain

13.1 Tricyclic antidepressants are more likely to cause increased appetite and weight gain than serotonin reuptake inhibitors. Irreversible monoamine oxidase inhibitors have a tendency to cause weight gain. Mirtazapine commonly causes increased appetite and significant weight gain. Serotonin-noradrenaline reuptake inhibitors have a minimal impact on weight. Fluoxetine has been associated with weight loss.

13.2 A weight gain advice leaflet is available on the Choice and Medication link on the intranet:


14 Hyperprolactinaemia

14.1 Long-standing increased plasma prolactin (with or without symptoms) is very occasionally seen with antidepressant use. When it does occur, rises of prolactin is usually small and short-lived and so symptoms are rare. Routine monitoring is not recommended. Where symptoms suggest the possibility of hyperprolactinaemia then the measurement of plasma prolactin is essential.

14.2 Where symptomatic hyperprolactinaemia is confirmed, a switch to mirtazapine is recommended.

14.3 There is a clear association observed between venlafaxine and prolactin elevation.

14.4 There are some reports in association with serotonin reuptake inhibitors and tricyclic antidepressants.

14.5 A leaflet is available on the Choice and Medication link on the intranet:

15 Pregnancy and breastfeeding

15.1 Patients who are already receiving antidepressants and are at high risk of relapse are best maintained on antidepressants during and after pregnancy6.

15.2 Those who develop a moderate or severe depressive illness during pregnancy should be treated with antidepressant medicines6.

15.3 Women should be advised on the spontaneous abortion rate in early pregnant (10-29%) and the baseline risk of congenital malformations (2-3%)6. Risk of medication in pregnancy and breastfeeding should be balanced against the risk to the foetus/baby of untreated maternal depression which includes adverse effects on obstetric outcomes, disrupted attachment, delayed infant/child development and vulnerability to subsequent mental health problems.

15.4 An individualised risk benefit analysis should take place when considering treatment and patients should be provided with written information to help them make an informed choice.

15.5 It is appropriate to consider using the lowest effective dose in pregnancy and breastfeeding. Polypharmacy should be avoided.

15.6 In terms of choice of antidepressant, refer to a current copy of the Maudsley prescribing guidelines. Paroxetine may be less safe than other SSRIs. When taking in late pregnancy, SSRIs and SNRIs may increase the risk of persistent pulmonary hypertension of the newborn6,19. Sertraline has a low infant exposure6. Sertraline is currently the SSRI of choice in pregnancy.

15.7 When choosing an antidepressant, consider the woman’s previous response to these medicines, stage of pregnancy, what is known about the reproductive safety of these medicines or alternative explanations and the risk of discontinuation symptoms and neonatal adaptation syndrome20.

15.8 Patients should be screened for alcohol use and for the development of hypertension and pre-eclampsia. Women who take serotonin reuptake inhibitors may be at an increased risk of post-partum haemorrhage6.

15.9 For a woman with moderate or severe depression in pregnancy or the postnatal period, a serotonin reuptake inhibitor, serotonin-noradrenaline reuptake inhibitor or a tricyclic antidepressant should be considered if she understands the risks associated with medication and she has expressed a preference for medication, she declined psychological interventions, her symptoms have not responded to psychological interventions or a combination of a high intensity psychological intervention with medication if there was a limited response to either intervention on their own20.

15.10 For a woman with a history of severe depression, presenting with mild depression in pregnancy or the postnatal period, a serotonin reuptake inhibitor, serotonin-noradrenaline reuptake inhibitor or a tricyclic antidepressant should be considered20.
15.11 Stopping treatment

Treatment should not be stopped abruptly and should not routinely be stopped. Below is guidance if there is good reason to stop treatment. The woman should also be advised not to stop treatment without medical supervision.

<table>
<thead>
<tr>
<th>Severity of depression</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild/moderate depression: treatment with serotonin reuptake inhibitor, serotonin-</td>
<td>Consider stopping gradually with facilitated self-help.</td>
</tr>
<tr>
<td>noradrenaline reuptake inhibitor or a tricyclic antidepressant</td>
<td></td>
</tr>
<tr>
<td>Moderate depression with a prescription for serotonin reuptake inhibitor, serotonin-</td>
<td>The previous response, stage of pregnancy, risk of relapse, risk associated with medication,</td>
</tr>
<tr>
<td>noradrenaline reuptake inhibitor or a tricyclic antidepressant</td>
<td>patient preference should be considered. The following alternatives should be considered –</td>
</tr>
<tr>
<td></td>
<td>high intensity psychological intervention or changing to a medicine that is effective with</td>
</tr>
<tr>
<td></td>
<td>a lower risk of adverse effects.</td>
</tr>
<tr>
<td>Severe depression with a prescription for serotonin reuptake inhibitor, serotonin-</td>
<td>The previous response, stage of pregnancy, risk of relapse, risk associated with medication,</td>
</tr>
<tr>
<td>noradrenaline reuptake inhibitor or a tricyclic antidepressant</td>
<td>patient preference should be considered. The following alternatives should be considered –</td>
</tr>
<tr>
<td></td>
<td>continuing the current medication, changing to a medicine that is effective with a lower risk</td>
</tr>
<tr>
<td></td>
<td>of adverse effects, combination treatment with high intensity psychological intervention or</td>
</tr>
<tr>
<td></td>
<td>switching to high intensity psychological therapy if the woman decides to stop taking</td>
</tr>
<tr>
<td></td>
<td>medication.</td>
</tr>
</tbody>
</table>
15.12 The neonate may experience discontinuation symptoms such as agitation and irritability or even respiratory distress and convulsions (with SSRIs). The risk is assumed to be particularly high with short half-life medicines such as venlafaxine and paroxetine. Continuing to breastfeed and then ‘weaning’ by switching to mixed (breast/bottle) feeding may help reduce the severity of the reactions.

15.13 The most up to date evidence should be obtained including new information e.g. a recent study found an association between prenatal use of SSRI antidepressants and autism risk in boys but did not prove cause-and-effect.

15.14 When assessing the risks and benefits of antipsychotic medication for a pregnant woman, the risk of gestational diabetes and excessive weight gain and the limited data of safety for antipsychotics in pregnancy and postnatal period should be taken into account. Pregnant women taking antipsychotic medication should be advised about diet and weight gain should be monitored, in line with the guideline on weight management before, during and after pregnancy. Monitor for gestational diabetes in pregnant women taking antipsychotic medication in line with the guideline on diabetes in pregnancy and offer an oral glucose tolerance test. Prolactin levels should be monitored in women who are taking prolactin-raising antipsychotic medication and planning a pregnancy, because raised prolactin levels reduce the chances of conception. A prolactin-sparing antipsychotic should be considered if prolactin levels are raised.

15.15 Benzodiazepines should not be offered to women in pregnancy and the postnatal period except for the short-term treatment of severe agitation.

15.16 Consider gradually stopping benzodiazepines in women who are planning a pregnancy, pregnant or considering breastfeeding.

15.17 Lithium is a human teratogen. Women of child-bearing age should be advised to use a reliable form of contraception. Lithium should not be offered to women who are planning a pregnancy or pregnant, unless antipsychotic medication has not been effective. If antipsychotic medication has not been effective and lithium is offered to a woman who is planning a pregnancy or pregnant, the woman should be advised:

- There is a risk of foetal heart malformations (Ebstein’s anomaly, atrial and ventricular septal defects) when lithium is taken in the first trimester, but the size of the risk is uncertain.
- That lithium levels may be high in breast milk with a risk of toxicity for the baby.
- Lithium levels should be monitored more frequently throughout pregnancy and the postnatal period.

15.18 The period of maximum risk to the foetus is 2-6 weeks after conception before many women know they are pregnant.

15.19 If a woman taking lithium becomes pregnant, consider stopping the medicine gradually over 4 weeks if she is well. It should be explained that stopping medication may not remove the risk of foetal heart malformations and that there is a risk of relapse.

15.20 If a woman taking lithium becomes pregnant and is not well or is at high risk of relapse, consider: switching gradually to an antipsychotic or stopping lithium and restarting it in the second trimester (if the woman is not planning to breastfeed and her symptoms...
have responded better to lithium than to other medicines in the past) or continuing with lithium if she is at high risk of relapse and an antipsychotic is unlikely to be effective\textsuperscript{20}.

**15.21 If a woman continues taking lithium during pregnancy:**

- an increasing dose of lithium is required to maintain the lithium level during pregnancy as total body water increases, but requirements return to pre-pregnancy levels immediately after delivery\textsuperscript{6}.
- high resolution ultrasound and echocardiography should be performed at 6 and 18 weeks of gestation to screen for Ebstein’s anomaly\textsuperscript{6}.
- check plasma lithium levels every 4 weeks, then weekly from the 36th week\textsuperscript{20}.
- adjust the dose to keep plasma lithium levels in the woman's therapeutic range\textsuperscript{20}.
- ensure the woman maintains an adequate fluid balance\textsuperscript{20}.
- ensure the woman gives birth in hospital\textsuperscript{20}.
- ensure monitoring by the obstetric team when labour starts, including checking plasma lithium levels and fluid balance because of the risk of dehydration and lithium toxicity\textsuperscript{20}.
- stop lithium during labour and check plasma lithium levels 12 hours after her last dose\textsuperscript{20}.
15.22 Neonatal goitre, hypotonia, lethargy and cardiac arrhythmia can occur in association with lithium.

15.23 Useful sources of information are an up to date copy of the Maudsley prescribing guidelines and Toxbase.

15.24 When assessing the risks and benefits of antidepressants for a woman is considering breastfeeding, the benefits of breastfeeding for the woman and baby, how medication may affect the woman’s ability to care for her baby, the uncertainty about the safety of these medicines for the breastfeeding baby and the risks associated with switching from or stopping a previously effective medicine should be considered.

15.25 The advice from a perinatal specialist should be sought.

15.26 See the ‘Choice and Medication’ link for pregnancy leaflets: http://www.choiceandmedication.org/candi/pages/printableleaflets/.

16 Interactions of serotonin re-uptake inhibitors (SSRIs) with other medicines

16.1 Fluoxetine, fluvoxamine and paroxetine are associated with a higher propensity for medicine interactions than other SSRIs.

16.2 SSRIs should not be normally offered to patients taking non-steroidal medicines because of the increased risk of gastrointestinal bleeding. Offer an antidepressant with a lower propensity to cause this e.g. mianserin, mirtazapine, moclobemide, reboxetine or trazodone. If a suitable alternative cannot be identified, a gastroprotective medicines should be prescribed concurrently with the SSRI.

16.3 SSRIs should not normally be offered to patients prescribed warfarin, aspirin or heparin because of their anti-platelet effect. Mirtazapine can be offered when taken with warfarin. The international normalised ratio (INR) may be increased slightly.

16.4 If aspirin is used as a single agent, mirtazapine, mianserin, trazodone or reboxetine can also be offered. If a suitable alternative cannot be identified, a gastroprotective medicines should be prescribed concurrently with the SSRI.

16.5 SSRIs should not normally be offered to patients prescribed triptan medicine for migraine. Mianserin, mirtazapine or trazodone can be offered. Fluoxetine or paroxetine should not be offered to patients prescribed atomoxetine. A different SSRI can be offered.

16.6 SSRIs should not be offered at the same time as a monoamine oxidase B inhibitor e.g. selegiline or rasagiline. Mirtazapine, mianserin, reboxetine, or trazodone can be offered.

16.7 Do not normally offer fluvoxamine to patients taking theophylline, clozapine, methadone or tizamidine. Offer a safer alternative such as sertraline or citalopram.

16.8 Do not offer fluoxetine or paroxetine to patients taking atomoxetine. Offer a different SSRI.

16.9 Sertraline is a preferred antidepressant for patients prescribed flecainide or propafenone, although mirtazapine or moclobemide can be used.
17 Interactions of mono-amine oxidase inhibitors (MAOIs)

17.1 All MAOIs have the potential to induce hypertensive crisis if foods containing tyramine (which is also metabolised by monoamine oxidase) are eaten or medicines that increase monoamine neurotransmission are co-prescribed, e.g. alcohol, opioids, antidepressants, levodopa and buspirone. These foods and medicines must be avoided for at least fourteen days after discontinuing MAOIs. The reversible inhibitors of monoamine oxidase (moclobemide) have a much lower likelihood of causing a hypertensive crisis and dietary restrictions are usually not required4,5.

17.2 If swapping from an antidepressant to a monoamine oxidase inhibitor, the gap varies depending on the half-life of the antidepressant (usually two weeks). If swapped from fluoxetine, then the gap should be five to six weeks5.

18 References

19 Dissemination and implementation arrangements

This document will be circulated to all managers who will be required to cascade the information to members of their teams. It will be available to all staff via the Foundation Trust intranet.

20 Training requirements

Staff will be provided training in how to use this policy in line with the Trust’s Mandatory Training Policy and the Learning and Development Guide. For training requirements please refer to the Trust’s Mandatory Training Policy and Learning and Development Guide.

21 Monitoring and audit arrangements

See table below.

22 Review of the policy

2 years – September 2018
<table>
<thead>
<tr>
<th>Element to be monitored</th>
<th>Lead</th>
<th>How Trust will monitor compliance</th>
<th>Frequency</th>
<th>Reporting arrangements</th>
<th>Acting on recommendations and Lead(s)</th>
<th>Change in practice and lessons to be shared</th>
</tr>
</thead>
<tbody>
<tr>
<td>See list of NHSLA minimum requirements if relevant</td>
<td>Chief Pharmacist</td>
<td>ePACT data Clinical pharmacy checks</td>
<td>ongoing</td>
<td>Drugs and Therapeutics Committe</td>
<td>Drugs and Therapeutics Group</td>
<td>Review of policy; implementation practices and procedures. Re- audit Give feedback to prescribers.</td>
</tr>
<tr>
<td>Formulary adherence</td>
<td></td>
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</tr>
</tbody>
</table>
23.0 Appendix 1

**Medicines not recommended in the management of depression**

19.1 Dosulepin (dothiepin) should not be initiated. Although it has similar efficacy to other antidepressants, this is outweighed by increased cardiac risk and toxicity in overdose.¹

19.2 The following drugs should be avoided as augmenting strategies as there is insufficient for their use: carbamazepine, lamotrigine, buspirone, pindolol, valproate or thyroid supplementation¹.

19.3 Augmentation of an antidepressant with a benzodiazepine for more than two weeks should not be used routinely as there is a risk of dependence¹.

19.4 Duloxetine should not be initiated. It is non-formulary in Trust. If the patient is already taking duloxetine, prescribers should review the need to continue the treatment. If it is deemed necessary, an application should be made via the Trust non-formulary process. Duloxetine may cause an exacerbation of hypertension¹.

19.5 St John’s wort may be benefit in mild or moderate depression. However, prescribers should not prescribe or advise the use St John’s wort by people with depression because of uncertainty about appropriate doses, persistence of effect, variation in the nature of preparations and potential serious interactions with other medicines (including oral contraceptives, anticoagulants and anticonvulsants). Prescribers should also advise patients with depression of the different potencies of the preparations available and of the potential serious interactions of St John’s wort with other medicines¹.
<table>
<thead>
<tr>
<th>From</th>
<th>Agomelatine</th>
<th>Bupropion</th>
<th>Clomipramine</th>
<th>Fluoxetine</th>
<th>Fluvoxamine</th>
<th>MAOIs phenelzine, tranylcypromine, selegiline</th>
<th>Moclobemide</th>
<th>Mirtazapine</th>
<th>Reboxetine</th>
<th>Trazodone</th>
<th>Other SSRIs, vortioxetine</th>
<th>SNRs duloxetine, venlafaxine</th>
<th>TCAs (except clomipramine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agomelatine</td>
<td>Stop agomelatine then start bupropion</td>
<td>Stop agomelatine then start clobamipramine</td>
<td>Stop agomelatine then start fluoxetine</td>
<td>Stop agomelatine then start fluvoxamine</td>
<td>Stop agomelatine then start MAOIs</td>
<td>Stop agomelatine then start moclobemide</td>
<td>Stop agomelatine then start mirtazapine</td>
<td>Stop agomelatine then start reboxetine</td>
<td>Stop agomelatine then start trazodone</td>
<td>Stop agomelatine then start SSRI</td>
<td>Stop agomelatine then start SNRI</td>
<td>Stop agomelatine then start TCA</td>
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<tr>
<td>Bupropion</td>
<td>Cross-taper cautiously</td>
<td>Cross-taper cautiously low dose clomipramine</td>
<td>Cross-taper cautiously low dose clomipramine</td>
<td>Taper and stop then start fluoxetine at 10mg/day</td>
<td>Taper and stop then wait for 2 weeks then start MAOIs</td>
<td>Taper and stop then wait for 2 weeks then stop moclobemide</td>
<td>Taper and stop then wait for 1 week then start moclobemide</td>
<td>Taper and stop then wait for 3 weeks then start MAOIs</td>
<td>Taper and stop then wait for 1 week then start moclobemide</td>
<td>Cross-taper cautiously low dose trazodone</td>
<td>Taper and stop then start low dose SNRI</td>
<td>Cross-taper cautiously low dose TCA</td>
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<td>Clomipramine</td>
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<td>Cross-taper cautiously</td>
<td>Cross-taper cautiously</td>
<td>Taper and stop then start fluoxetine</td>
<td>Taper and stop then wait for 3 weeks then start MAOIs</td>
<td>Taper and stop then wait for 5-6 weeks then start MAOIs</td>
<td>Taper and stop then wait for 5-6 weeks then start moclobemide</td>
<td>Taper and stop then wait for 4-7 days then start low dose trazodone</td>
<td>Taper and stop then start low dose</td>
<td>Taper and stop then start low dose SNRI</td>
<td>Taper and stop then start low dose SNRI</td>
<td>Cross-taper cautiously</td>
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<tr>
<td>Fluoxetine</td>
<td>Cross-taper cautiously</td>
<td>Cross-taper cautiously</td>
<td>Cross-taper cautiously</td>
<td>Taper &amp; stop fluoxetine. Wait 2 weeks. Start low dose clomipramine</td>
<td>Taper and stop. Wait 2 weeks then start low dose fluvoxamine</td>
<td>Taper and stop then wait for 5-6 weeks then start MAOIs</td>
<td>Taper and stop then wait for 5-6 weeks then start moclobemide</td>
<td>Cross-taper cautiously low dose trazodone</td>
<td>Taper and stop then start low dose</td>
<td>Taper and stop then start low dose SNRI</td>
<td>Taper and stop then start low dose SNRI</td>
<td>Cross-taper cautiously low dose TCA</td>
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<td>Fluvoxamine</td>
<td>Taper and stop then wait for 1 week</td>
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<td>Cross-taper cautiously low dose clomipramine</td>
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<td>Taper and stop then start fluvoxamine</td>
<td>Taper and stop then wait for 1 week then start MAOIs</td>
<td>Taper and stop then wait for 1 week then start moclobemide</td>
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<td>Taper and stop then start low dose SSRI</td>
<td>Taper and stop then start low dose SNRI</td>
<td>Taper and stop then start low dose SNRI</td>
<td>Cross-taper cautiously low dose TCA</td>
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<td>MAOIs phenelzine, tranylcypromine, selegiline</td>
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<td>Cross-taper cautiously</td>
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<td>Taper and stop then start fluoxetine</td>
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<td>Taper and stop then wait 2 weeks</td>
<td>Taper and stop then wait 2 weeks</td>
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<td>Mirtazapine</td>
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<td>Reduce over 4 weeks</td>
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<td>Taper and stop over 4 weeks if necessary</td>
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<td>Other SSRIs, vortioxetine</td>
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<td>Taper and stop over 1 week if necessary</td>
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<td>SNRIs, duloxetine, venlafaxine</td>
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<tr>
<td>TCAs</td>
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<td>Taper and stop over 1 week if necessary</td>
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<tr>
<td>Stopping</td>
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<td>Cross-taper cautiously</td>
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</tbody>
</table>
25. Appendix 3:

Practice based mental health team:
cim-tr.PCMH@nhs.net – practice based mental health team

Mental health assessment and advice team:
cim-tr.aat-referrals@nhs.net - AAT

Tel: 02033177300