ANTIDEPRESSANT GUIDELINES

TREATMENT OF DEPRESSION
Authors:

Ms Diane Booth, Chief Pharmacist, Berkshire Healthcare NHS Foundation Trust.

Mrs Kiran Hewitt, Lead Clinical Pharmacist, Berkshire Healthcare NHS Foundation Trust.

Mrs Katie Sims, Senior Clinical Pharmacist, Berkshire Healthcare NHS Foundation Trust.

Mr Alastair Raynes, Medicines Information Lead Pharmacist, Berkshire Healthcare NHS Foundation Trust

Acknowledgements:

The authors would like to thank the members of the pharmacy department, Prospect Park Hospital and the Medicines Management Committee representatives of Berkshire Healthcare NHS Foundation Trust who provided help, advice and constructive feed back during the compilation of these guidelines.

Any enquiries regarding these guidelines or other medication related queries should be forwarded to the MI (Medicines Information) Service, pharmacy department, Prospect Park Hospital, on 0118 960 5075/5059, or your ward/locality pharmacist.
## CONTENTS

### ANTIDEPRESSANT GUIDELINES

**TREATMENT OF DEPRESSION**

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicines Formulary</td>
<td>4</td>
</tr>
<tr>
<td>Treatment Choices</td>
<td>4</td>
</tr>
<tr>
<td>Treatment Algorithm</td>
<td>6</td>
</tr>
<tr>
<td>Factors Affecting Choice</td>
<td>8</td>
</tr>
<tr>
<td>General Treatment Principles</td>
<td>10</td>
</tr>
<tr>
<td>Additional Information/Guidance</td>
<td>11</td>
</tr>
<tr>
<td>Clinical Information</td>
<td>11</td>
</tr>
<tr>
<td>Treatment Options for Special Populations</td>
<td>12</td>
</tr>
<tr>
<td>Antidepressant-Induced Sexual Dysfunction</td>
<td>13</td>
</tr>
<tr>
<td>Hyponatraemia</td>
<td>14</td>
</tr>
<tr>
<td>Serotonin Syndrome</td>
<td>14</td>
</tr>
<tr>
<td>Switching &amp; Stopping</td>
<td>15</td>
</tr>
<tr>
<td>Treatment Resistance</td>
<td>17</td>
</tr>
<tr>
<td>St John’s Wort</td>
<td>20</td>
</tr>
<tr>
<td>Interactions of SSRIs with other medication</td>
<td>22</td>
</tr>
<tr>
<td>SSRIs – licensed indications</td>
<td>23</td>
</tr>
<tr>
<td>Using Antidepressants in Children and Young People</td>
<td>24</td>
</tr>
<tr>
<td>Antidepressants in pregnancy</td>
<td>25</td>
</tr>
<tr>
<td>Antidepressants in breastfeeding</td>
<td>32</td>
</tr>
<tr>
<td>References</td>
<td>34</td>
</tr>
</tbody>
</table>
Antidepressants not approved by BHFT:

Escitalopram (Cipralex®)*
Agomelatine
Duloxetine

*Escitalopram (an SSRI) has been evaluated by BHFT’s Medicines Management Committee and has not been approved for use within the Trust. It therefore should not be prescribed for routine use until further notice. A consultant psychiatrist wishing to prescribe this antidepressant may only do so on a named patient basis and with approval from BHFT’s Pharmacy Department, following the completion and submission of the appropriate paperwork.
Antidepressant Guidelines

Escitalopram request form

At the Medicines Management Committee on 20/04/10 when the depression prescribing guidelines were reviewed in the light of NICE clinical guidelines 90 and 91 it was considered that the cost-benefit ratio for escitalopram did not warrant adding it to the formulary. However, its use may be justified for particular patients who are severely depressed and who have tried at least two other antidepressants at an adequate dose and duration.

Please fill in this form below and:
- **Inpatients:** send it to pharmacy along with the prescription for this medication. A copy should be filed in the patient’s notes.
- **On Discharge:** please send this form to the GP along with the normal paperwork so that they can keep it in the patient’s notes and show it to the PCT when questioned on their prescribing.
- **Outpatients:** please send this form to the GP along with the routine paperwork so that they can keep it in the patient’s notes and show it to the PCT when questioned on their prescribing.

Patient’s name:……………………………………………………………………DoB:……………………

Hamilton depression rating scale score when decision to initiate escitalopram made:……………………..

<table>
<thead>
<tr>
<th>Antidepressant tried</th>
<th>Dose Used</th>
<th>Duration on that dose (in weeks)</th>
<th>Reason for discontinuing (e.g. intolerance or lack of efficacy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4&lt;sup&gt;th&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5&lt;sup&gt;th&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6&lt;sup&gt;th&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Reason(s) for suggesting escitalopram:..............................................................................................

.................................................................

.................................................................

.................................................................

.................................................................

.................................................................

.................................................................

.................................................................

.................................................................

.................................................................

After eight weeks on escitalopram the patient must be reassessed for possible benefit. No further supplies will be made by the hospital pharmacy unless the rating scale score at eight weeks is received (and there is an improvement).

Hamilton depression rating scale score after 8 weeks on escitalopram:……………..

Dose of escitalopram after 8 weeks:……………………

Consultant’s name:………………………………………..

Date completed:………………………………………..
If you would like further advice about this please contact Medicines Information on 0118 960 5075 or at medicines.info@berkshire.nhs.uk
Antidepressant Guidelines

Depression – Drug Treatment Algorithm

Start antidepressant* and titrate (if necessary) to therapeutic dose. Assess** after 2 weeks¹

Review after 3-4 weeks¹

No / Minimal improvement

Some improvement

Increase support
Consider dose increase in line with SPC if tolerated¹

Side effect (s/e) or person prefers

Some improvement

Continue for further 2-4 weeks

Effective tolerated

Still ineffective or s/e or person prefers

Continue at therapeutic dose for at least 6 months after remission¹;² Continue for at least 2 years if at risk of relapse***+⁴†;⁵, and consider longer-term treatment. Withdraw slowly

Effective tolerated

Switch antidepressant⁶

- To an alternative SSRI OR a different class
- Assess over 3-4 weeks
- Consider a longer trial if multiple treatment failures³
- Contact MI for advice on how to switch

Effective tolerated

Ineffective

Check compliance

Review diagnosis including possibility of additional physical or psychiatric diagnoses requiring treatment

Refer to suggested treatments for treatment refractory depression

Not tolerated

Switch to an antidepressant from a different class.
Assess over 3-4 weeks
Consider a longer trial if multiple treatment failures

Ineffective

Primary care may refer for specialist advice at any point in the algorithm, but should ALWAYS refer after two failed attempts at treatment with antidepressants.

¹ Discuss choice of drug with the patient regarding adverse effects, therapeutic effects, discontinuation effects etc

² Assess after 1 week for those at risk of suicide or age under 30, and then frequently as necessary

³ At each review assess response, adherence to drug treatment, side effects, suicide risk

⁴ Tools such as the Montgomery Asberg depression rating scale (MADRS) and the Hamilton depression rating scale (HAM-D) are recommended to monitor the response and benefit.

⁵ *** Assess patients for risk factors for relapse. The most important are presence of residual symptoms, number of previous episodes, severity, duration and degree of treatment resistance of the current episode*

MI = Medicines Information service at Prospect Park Hospital
Tel: 0118-960-5075, Monday – Friday 9am – 5pm
Email: medicines.information@berkshire.nhs.uk

Berkshire Healthcare NHS Foundation Trust
Edition 6.2 Nov 2010
NICE Guidance on Depression (CG90)

The Stepped-care model

<table>
<thead>
<tr>
<th>Focus of the Intervention</th>
<th>Nature of the Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 4:</strong> Severe and complex depression; risk to life; severe self-neglect</td>
<td>Medication, high-intensity psychological interventions, electroconvulsive therapy, crisis service, combined treatments, multiprofessional and inpatient care</td>
</tr>
<tr>
<td><strong>Step 3:</strong> Persistent subthreshold depressive symptoms or mild to moderate depression with inadequate response to initial interventions; moderate and severe depression</td>
<td>Medication, high-intensity psychological interventions, combined treatments, collaborative care and referral for further assessment and interventions</td>
</tr>
<tr>
<td><strong>Step 2:</strong> Persistent subthreshold depressive symptoms; mild to moderate depression</td>
<td>Low-intensity psychological and psychosocial interventions, medication and referral for further assessment and interventions</td>
</tr>
<tr>
<td><strong>Step 1:</strong> All known and suspected presentations of depression</td>
<td>Assessment, support, psychoeducation, active monitoring and referral for further assessment and interventions</td>
</tr>
</tbody>
</table>

- Antidepressants are NOT recommended as first-line treatment in recent onset, mild depression or persistent subthreshold depressive symptoms. Active monitoring, individual guided self-help, CBT or exercise are preferred options. However, consider them for people with:
  - mild depression that complicates the care of a physical health problem
  - a past history of moderate or severe depression
  - initial presentation of subthreshold depressive symptoms that have been present for a long period (typically at least 2 years)
  - depression/depressive symptoms that persist after other interventions

- Antidepressants ARE recommended for the treatment of moderate to severe depression and for dysthymia.

- For severe depression, a combination of an antidepressant and CBT is recommended.

- The use of ECT is supported in severe and treatment-resistant depression

---

\(^a\) Complex depression includes depression that shows an inadequate response to multiple treatments, is complicated by psychotic symptoms, and/or is associated with significant psychiatric comorbidity or psychosocial factors.

\(^b\) Only for depression where the person also has a chronic physical health problem and associated functional impairment

MI = Medicines Information service at Prospect Park Hospital
Tel: 0118-960-5075, Monday – Friday 9am – 5pm
Email: medicines.info@berkshire.nhs.uk

Berkshire Healthcare NHS Foundation Trust
Edition 6.2 Nov 2010
Antidepressant Guidelines

When prescribing antidepressants, always consider:

- previous treatment response to a particular drug
- tolerability and adverse effects of a previously given drug
- likely side-effect profile
- risk of lethality in overdose if history or likelihood of overdose
- concurrent physical illness or condition that may make the antidepressant more noxious or less well-tolerated
- concurrent medication that may interact with the antidepressant drug
- associated psychiatric disorder that may specifically respond to a particular class of antidepressant (e.g. obsessive-compulsive disorder and SSRIs)
- patient preference

Careful monitoring of symptoms, side effects and suicide risk (particularly in those aged under 30) should be routinely undertaken, especially when initiating antidepressant medication.

Factors Affecting Choice of Antidepressant

According to NICE\(^1\), when an antidepressant is to be prescribed, it should normally be a generic SSRI because they are as effective as other antidepressants and have a favourable risk-benefit ratio. They are also less toxic in overdose. Also consider:

- SSRIs are associated with an increased risk of bleeding, especially in older people or in those taking other drugs that have the potential to damage the gastro-intestinal mucosa or interfere with clotting. In particular, consider prescribing a gastroprotective drug in older people who are taking NSAIDs/aspirin.
- Fluoxetine, fluvoxamine and paroxetine have a higher propensity for drug interactions.
- Sertraline or citalopram have a lower propensity for drug interactions and so may be useful for patients on multiple drug regimes.
- Paroxetine is associated with a higher incidence of discontinuation symptoms
- Fluoxetine is associated with a much lower incidence of discontinuation symptoms, due to its long half-life and that of its active metabolite. This may be useful for patients in whom compliance is a concern as there is a decreased likelihood of discontinuation effects from missed doses.
Antidepressant Guidelines

- There is minimal evidence to support increasing the dose of SSRIs in depression

- When prescribing drugs other than SSRIs, consider
  - The increased likelihood of the person stopping treatment because of side-effects, and the consequent need to increase the dose gradually with venlafaxine, duloxetine and TCAs.
  - Toxicity in overdose. The greatest risk is with TCAs (apart from lofepramine) but venlafaxine is also more dangerous in overdose than other newer antidepressants

- Where a TCA is chosen, lofepramine is least cardiotoxic compared with the others

- The specific cautions, C/Is and monitoring requirements for some drugs:

  For **venlafaxine**:

  - Should not be prescribed for those at high risk of serious cardiac arrhythmias, recent MI or uncontrolled hypertension (see MHRA website at www.mhra.gov.uk)⁷
  - Check BP on initiation and regularly thereafter, especially with doses over 200mg. For those experiencing sustained increases the dose should be reduced or the drug discontinued.
  - Specialist supervision is required in those requiring doses of 300mg daily or above
  - Note the high propensity for discontinuation symptoms

  For **TCAs** – potential for postural hypotension and arrhythmias
  For **mianserin** – the need for haematological monitoring in elderly people

  - The choice of second antidepressant can be from the same, or different, antidepressant classes. Although evidence for the former does exist, switching between classes is in practice, better accepted as being the more logical option.

  - In more severely ill patients after failure with other antidepressants, consider an older TCA, venlafaxine (at least 150mg/day) or escitalopram in preference to another SSRI or MAOI.³ N.B. Within BHFT, escitalopram use is restricted (see previous requirements for its use).
General Treatment Principles

- When an antidepressant is to be prescribed for a patient with depression and a chronic physical health problem, take into account the following:
  - the presence of additional physical health disorders
  - the side effects of antidepressants, which may impact on the underlying physical disease (in particular, SSRIs may result in or exacerbate hyponatraemia, especially in older people)
  - that there is no evidence as yet supporting the use of specific antidepressants for patients with particular chronic physical health problems
  - Interactions with other medications. Generally, SSRIs are the antidepressants of choice for depression associated with physical illness, in particular sertraline and citalopram, due to their lower interaction potential (see table on p.22)

- Discuss with the patient as appropriate:
  - their perception of the efficacy and tolerability of any antidepressants they have previously taken
  - the choice of drug
  - the likely gradual relief from symptoms over several weeks
  - the time course of treatment
  - the need to take medication as prescribed
  - side-effects
  - discontinuation symptoms
  - potential interactions with concomitant medication or physical health problems
  - how continuation after remission decreases the risk of relapse
  - the fact that addiction does not occur

- Treat adequately
  - adequate doses (N.B. although in more severely ill patients, 150mg-equivalent tricyclic doses may be beneficial, NICE CG90 states that patients with a clear clinical response on low dose tricyclics can be maintained on that dose with careful monitoring)
  - adequate assessment (assess and document treatment efficacy over 2-4 weeks, and longer if any previous treatment failure)
  - adequate treatment period after resolution of symptoms – at least 6 months for first episode depression. Patients with two prior episodes and functional impairment should be treated for at least 2 years.

- Initiate, withdraw and switch medication slowly to minimise side effects. Medicines Information can be contacted for advice concerning individual switches. Warn patients about side-effects and discontinuation symptoms.

- Patients started on antidepressants who are considered to present an increased suicide risk or are younger than 30 years (because of the potential increased suicide risk associated with the early stages of antidepressant treatment for this group) should normally be seen after 1 week and frequently thereafter as appropriate until the risk is no longer considered significant.
Consider contributory causes including infections, substance misuse, electrolyte imbalances, endocrine disorders e.g. hypothyroidism, malnutrition, CNS causes e.g. stroke, medication e.g. antihypertensives. Many can be ruled out with simple blood tests including full blood count, U&Es, B12/folate, liver function tests, thyroid function, urine/oral fluid testing for illicit drugs etc. It is important to recognise that some medicines and/or illness can make depression more likely.

## Antidepressants – Clinical Information

<table>
<thead>
<tr>
<th>Drug</th>
<th>Half-life (in hours)</th>
<th>Sexual dysfunction</th>
<th>Anticholinergic</th>
<th>Cardiac</th>
<th>Nausea</th>
<th>Sedation</th>
<th>Toxicity in Overdose</th>
<th>Proconvulsant Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tricyclics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>8-24 *</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>17-28 *</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Imipramine</td>
<td>4-18 *</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Lofepramine</td>
<td>1.6 *</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>7-23</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>SSRIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>33</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>30</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>24-140*</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>24</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sertraline</td>
<td>25-36 *</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>MAOIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenelzine</td>
<td>1.5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>2.5</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>8-17</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>20-40</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>1-2</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>?</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>13</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Trazodone</td>
<td>3-7</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>1-2*</td>
<td>++</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

Adapted and reproduced with permission from “Psychotropic Drug Directory” – Steve Bazire, 2009

**Key:**

+++ significant effect  
++  moderate effect  
+  mild effect  
0 little or minimal effect  
? no information or little reported
## Treatment of Special Patient Populations

<table>
<thead>
<tr>
<th>Condition/Population</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Choice</th>
<th>Alternative/2&lt;sup&gt;nd&lt;/sup&gt; Choice</th>
<th>Avoid</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>imipramine amitriptyline</td>
<td>SSRIs (N.B. Paroxetine may be less safe)</td>
<td></td>
<td>few data available. Please consult (MI) for specific information</td>
</tr>
<tr>
<td>Lactation</td>
<td>imipramine nortriptyline</td>
<td>sertraline paroxetine</td>
<td>doxepin</td>
<td>minimal data available. Consult MI for specific info</td>
</tr>
<tr>
<td>Cardio-vascular disease</td>
<td>sertraline</td>
<td>other SSRIs mirtazapine</td>
<td>tricyclics</td>
<td>trazodone, venlafaxine and lofepramine may sometimes be suitable. Consult MI for advice.</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>SSRIs moclobemide</td>
<td>tricyclics</td>
<td></td>
<td>consult pharmacy for details of interactions with anti-epileptic drugs <em>important</em> Very limited data and experience with newer agents</td>
</tr>
<tr>
<td>Liver disease</td>
<td>paroxetine</td>
<td>citalopram imipramine</td>
<td>tricyclics</td>
<td>dosage reduction often required. Other agents may be possible. Consult MI for advice.</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>citalopram sertraline</td>
<td>moclobemide paroxetine</td>
<td></td>
<td>dosage reduction may be required. Low dose tricyclics may be possibilities. Consult MI for advice.</td>
</tr>
<tr>
<td>Adolescence</td>
<td>fluoxetine</td>
<td>citalopram sertraline</td>
<td>paroxetine venlafaxine tricyclics St.Johns Wort fluvoxamine</td>
<td>specialist advice required. Most drugs will not be licensed for this age group.</td>
</tr>
<tr>
<td>Old age</td>
<td>SSRIs moclobemide</td>
<td>venlafaxine lofepramine mirtazapine</td>
<td>MAOIs tricyclics (generally)</td>
<td>Changes in absorption, distribution, metabolism and excretion- adverse effects more likely.– start low, go slow, monitor effects</td>
</tr>
</tbody>
</table>

* has active metabolite with prolonged half-lives
Antidepressant-Induced Sexual Dysfunction

Most antidepressants can cause sexual dysfunction. Mechanisms involved include indirect effects such as sedation, hormonal effects, inhibition of nitric oxide and specific actions on neurotransmitters, such as serotonin and cholinergic/adrenergic balance. A thorough assessment is essential to exclude physical causes such as diabetes and cardiovascular disease, and psychological and relationship difficulties. Problems reported are wide-ranging, including lowered libido, impotence and delayed, or inhibited orgasm. Occasionally these effects can be utilised therapeutically, for example SSRIs can be used to treat premature ejaculation, as they tend to delay orgasm.

Drug-induced sexual dysfunction can be managed in several ways, including:

- reducing the dose of the antidepressant where possible, or consider discontinuing it.
- continued monitoring, as in around 10% of cases, spontaneous remission occurs, and in a further 11% partial remission occurs without intervention.
- changing to an antidepressant less likely to cause that specific problem. Please contact pharmacy’s medicines information service to discuss. Depending on the problem, options may include moclobemide, reboxetine or mirtazapine. These may have lower incidences of problems generally (see clinical information table).
- a prolactin level may be useful e.g. where a patient is taking several psychotropic agents and it is difficult to determine which are the likely causes. High prolactin levels with many antipsychotics can cause various types of sexual dysfunction in addition to menstrual problems and other effects.

Less routinely, other strategies are available.

- “Drug holidays” which involve withdrawing medication for short periods (e.g. at the weekend) may cause further problems, such as discontinuation symptoms or relapse.
- Sildenafil is more effective than placebo at improving sexual function in men, and in improving sexual function in women taking SSRIs. However, this cannot be funded by BHFT and would require GP involvement.
- A Cochrane review of the strategies for managing sexual dysfunction induced by antidepressant medication, found that the addition of sildenafil, tadalafil or bupropion may improve sexual function but that other augmentation strategies did not.

Contact MI for further information.
CSM Advice – Hyponatraemia

“Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants and should be considered in all patients who develop drowsiness, confusion or convulsions while taking an antidepressant”²⁴

All patients taking antidepressants should be observed for signs of hyponatraemia e.g. dizziness, nausea, lethargy, confusion, cramps and seizures. In addition, consider regular monitoring of serum sodium for those at high risk¹¹ i.e.:–

- extreme old age
- history of hyponatraemia
- co-therapy with other drugs known to cause hyponatraemia e.g. carbamazepine, gabapentin, lamotrigine, valproate, vigabatrin, buspirone, zopiclone, lithium and antipsychotics.
- reduced renal function
- medical co-morbidity

Treatment will depend on the extent of the hyponatraemia and condition of the patient. However, the antidepressant should be withdrawn immediately. When re-starting treatment, choose an anti-depressant from a different class.

Serotonin Syndrome

Serotonin syndrome is due to excess serotonin (5-HT) availability in the CNS, usually occurring when two or more serotonergic agents are co-administered, although it has occurred with a single drug. Cases frequently involve an MAOI, SSRI, tryptophan and clomipramine. Onset is usually within a few hours of drug increases/changes. Cases are often undiagnosed as symptoms may be mild and self-limiting, but severe cases and deaths have been reported.⁹

Sternbach’s Diagnostic Criteria: ²⁵

- Appearance of symptoms should bear a temporal link to the addition of, or dose increase of a serotonergic agent
- At least three of the following must be present – mental state changes (e.g. confusion, hypomania), agitation, myoclonus, hyperreflexia, sweating, shivering, tremor, diarrhoea, incoordination, fever
- Other causes (e.g. infection, drug abuse or withdrawal) have been excluded
- An antipsychotic has not been started or increased in dosage prior to the onset of symptoms (to avoid confusion with NMS)

Treatment

Mild cases tend to resolve within 24 hours, with drug discontinuation. Treatment is supportive, depending on the presentation²⁶; benzodiazepines may help. Severe
cases may require serotonin antagonists such as cyproheptadine or propranolol, although these agents have not been formally tested. Contact MI for advice.

Serotonin syndrome can often be prevented by avoiding the use of more than one serotonergic drug in combination. In addition, extra care should be taken when changing from one anti-depressant to another – contact pharmacy for advice or use established guidelines. These may advise washout periods and take into consideration drug interactions and drug half-lives (see below).

Antidepressants – Switching & Stopping

Switching

When switching from one antidepressant to another, abrupt withdrawal of a drug should be avoided to avoid discontinuation side effects, unless a serious adverse event has occurred.

“Cross tapering” is usually recommended, where the dose of the redundant drug is slowly reduced, and the new agent is introduced. No clear guidelines are available for this, and caution is always advisable. The speed of cross-tapering is best judged by patient tolerability. However, co-administration of some antidepressants is strictly contra-indicated – e.g. MAOIs and SSRIs. In some cases, cross tapering may not be necessary. For example, when switching from one SSRI to another, the effects may be similar enough that the second drug may ameliorate the withdrawal effects of the first.

Potential problems include:

- pharmacodynamic interactions such as serotonin syndrome and sedation
- pharmacokinetic interactions e.g. elevation of tricyclic levels by SSRIs.
- cholinergic rebound e.g. headache, nausea and vomiting from withdrawal of drugs blocking cholinergic receptors e.g. tricyclics
- Antidepressant discontinuation symptoms, including discontinuation effects from the first drug being interpreted as side-effects from the second

When selecting a regimen for switching drugs, a number of factors must be taken into consideration: 9

- speed – faster switches may need more monitoring and caution
- current dose of the first drug
- individual drugs and their effects – e.g. on neurotransmitters, half-lives – e.g. if the first drug has a long half-life, any interaction may be prolonged for some time after its withdrawal
- individual susceptibility to additive side effects
- patient tolerability – the speed of the switch depends on what the patient can tolerate in terms of side effects

Please consult pharmacy's medicines information service for specific switching advice.
Stopping: Discontinuation Syndrome

The term “discontinuation syndrome” describes the range of symptoms that can be experienced on stopping prescribed drugs which are not drugs of dependence.

Discontinuation symptoms may be new, or hard to distinguish from some of the original symptoms of the underlying illness. They are experienced by at least one third of patients taking antidepressant drugs. Symptoms may also be mistaken for a relapse of illness or the emergence of a new physical illness, leading to unnecessary interventions.

All patients should be informed when treatment is commenced that although not addictive, discontinuation symptoms may occur by stopping, missing doses or reducing the dose of the antidepressant and can usually be avoided by withdrawing slowly over at least four weeks.

Discontinuation symptoms have a number of characteristics:

- 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)
- They often resolve within 24 hours of restarting the drug
- They are usually mild and self-limiting, but can occasionally be severe and prolonged
- Risk is higher in those taking antidepressants for eight weeks or longer in those prescribed short half-life drugs, those who developed anxiety symptoms at the start of therapy, those receiving other centrally acting medication and in children and adolescents who have experienced discontinuation symptoms before.

Some symptoms are characteristic of the different groups of antidepressant drugs:

<table>
<thead>
<tr>
<th>Discontinuation Symptoms</th>
<th>MAOIs</th>
<th>Tricyclics</th>
<th>SSRIs and Venlafaxine</th>
</tr>
</thead>
<tbody>
<tr>
<td>agitation</td>
<td>“flu”-like symptoms (chills, myalgia, excessive sweating, headache, nausea)</td>
<td>“flu”-like symptoms “shock-like” sensations dizziness (exacerbated by movement) insomnia excessive dreaming</td>
<td></td>
</tr>
<tr>
<td>irritability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ataxia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>movement disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>insomnia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>somnolence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vivid dreams</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cognitive impairment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>slowed speech</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pressured speech</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occasional hallucinations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>paranoid delusions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occasional movement disorders mania</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occasional movement disorders problems with</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Withdraw antidepressants over at least 4 weeks, e.g. by halving the dose at weekly intervals, in order to minimise the risk of discontinuation symptoms.

- The shorter the half-life of the drug, the more important that this rule is followed.
- Patients receiving long-term maintenance treatment should have the dose reduced over a longer period – e.g. by 25% every four to six weeks.\(^{30}\)
- The end of the taper may need to be slower, as symptoms may not appear until the reduction in the daily dosage is substantial.
- Patients receiving MAOIs may need to be tapered over a longer period.
- If withdrawal symptoms occur, the rate of withdrawal may be slowed.
- The only exception is fluoxetine. Due to the long plasma half-life of this drug (i.e. 24–140 hours plus 168–216 for the active metabolite norfluoxetine), withdrawal reactions are extremely rare, and so abrupt discontinuation should not pose any problems.
- If symptoms are mild, reassure the patient that it will pass in a few days, and is not uncommon. If symptoms are severe, reintroduce the original antidepressant and taper gradually while monitoring for symptoms.\(^{28}\)
- Some patients find that slow tapering may not reduce the severity of discontinuation reactions, and actually prefer abrupt cessation and a shorter discontinuation syndrome.

### Treatment Resistant Depression

Around one third of patients treated for major depression do not respond satisfactorily to first-round antidepressant therapy. It is difficult to evaluate the true level of resistance due to the inconsistent way it is characterised and defined.

According to NICE\(^1\), for a person whose depression has not responded to either pharmacological or psychological interventions, consider combining antidepressant medication with CBT.

Before using strategies for treatment-resistant depression:

- check dose, side-effects and compliance
- consider re-introducing previous treatments that have been inadequately delivered or adhered to, including increasing the dose
- consider switching to an alternative antidepressant
- review diagnosis
- exclude physical causes – thyroid disorder, anaemia, folate deficiency, electrolyte imbalances etc.
- consider co-morbidity e.g. personality disorder, alcohol/drug abuse
- increase the frequency of appointments
A wide range of strategies have been employed, many of which have a very weak evidence-base. Some of the first choice treatments for which there is reasonable published support, are shown in the table below:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add lithium, aiming for a level of 0.4-1.0mmol/l</td>
<td>Sound evidence base Effective in around 50% cases Recommended by NICE</td>
<td>Less acceptable to patients Potentially toxic drug requiring plasma level monitoring and specialist initiation</td>
</tr>
<tr>
<td>Add atypical antipsychotic i.e. olanzapine, aripiprazole, risperidone or quetiapine</td>
<td>Some good evidence e.g. olanzapine/fluoxetine combination, and some RCTs e.g. aripiprazole Usually well tolerated</td>
<td>Developing evidence base Side-effect burden of atypical antidepressant to consider Patients more likely to leave treatment early due to side-effects</td>
</tr>
<tr>
<td>ECT</td>
<td>Effective Well-documented in literature</td>
<td>Poor public perception Needs general anaesthetic Specialist referral</td>
</tr>
<tr>
<td>Add tri-iodothyronine (20-50mcg/day)</td>
<td>Reasonable support in literature Well tolerated Recent interest following STAR-D trial</td>
<td>Requires monitoring Caution in cardiovascular disease Most evidence is with tricyclics Requires specialist referral Prolonged treatment may lead to hypothyroidism on discontinuation NICE conclude that the evidence is inconsistent and do not recommend this as a routine strategy</td>
</tr>
<tr>
<td>Add mirtazapine 30-45mg/d or mianserin 30mg/d to an SSRI (or venlafaxine)</td>
<td>Recommended by NICE Generally well-tolerated Gaining more widespread use</td>
<td>More side-effects with combination treatment Most data with mianserin Risk of blood dyscrasia with mianserin Risk of serotonin syndrome</td>
</tr>
</tbody>
</table>

MI = Medicines Information service at Prospect Park Hospital
Tel: 0118-960-5075, Monday – Friday 9am – 5pm
Email: medicines.information@berkshire.nhs.uk
Berkshire Healthcare NHS Foundation Trust
Edition 6.2 Nov 2010
### Second-line/Alternatives with less supporting evidence

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose venlafaxine (over 200mg/day)(^{34})</td>
<td>Could be initiated in primary care&lt;br&gt;Well tolerated</td>
<td>Limited evidence&lt;br&gt;Requires blood pressure monitoring</td>
</tr>
<tr>
<td>Add pindolol 2.5mg tds - up to 5mg tds(^{35})</td>
<td>Well tolerated</td>
<td>Uncertainty regarding optimum dose and duration&lt;br&gt;Contradictory results&lt;br&gt;Data mainly relate to acceleration of response</td>
</tr>
<tr>
<td>Add tryptophan 2-3g tds(^{36})</td>
<td>Use documented widely&lt;br&gt;Well tolerated</td>
<td>Secondary care only.&lt;br&gt;Data relate mainly to tricyclics/MAOIs&lt;br&gt;Weak evidence base</td>
</tr>
</tbody>
</table>

Combining antidepressants with different modes of action is often used, but not routinely recommended. There is very little evidence for this practice, and toxicity may be additive. Both pharmacokinetic and pharmacodynamic interactions must be considered. For example, certain SSRIs may unpredictably increase tricyclic levels which can be extremely hazardous. Combinations of serotonergic antidepressants increase the risk of developing serotonin syndrome, which could be fatal. Only combinations which have an evidence base should be considered, such as an SSRI (or venlafaxine) + mirtazapine.

### When using combinations of medications:

- choose medications that are known to be safe when used together, and have some supporting evidence
- be aware of the increased side-effect burden
- discuss the rationale for any combination with the person with depression, follow GMC guidance if off-label medication is prescribed, and monitor carefully for adverse effects
- be familiar with primary evidence and consider obtaining a second opinion when using unusual combinations, the evidence for the efficacy of a chosen strategy is limited or the risk–benefit ratio is unclear
- document the rationale for the chosen combination.

Please contact MI for details of possible combinations and to discuss individual cases.
St John’s Wort (Hypericum Perforatum)

St. John’s Wort (SJW) is the common name for the plant hypericum perforatum, used for centuries for medicinal purposes, including treating depression. It is not licensed in the UK as a medicine but can be bought “over the counter” from health food shops, herbalists and pharmacies.

It is known to contain at least ten constituents or groups of components that may contribute to its pharmacological effects but its exact mode of action is unknown. At one time, monoamine oxidase inhibition was thought to be the most likely mechanism, but probably only accounts for a small proportion of its activity. In common with all herbal preparations, the quantity and proportions of each constituent varies between batches. Most commercial products are standardised with respect to hypericin content but it is not known if this is the only active component. Individual brands or batches of the same brand may therefore not be therapeutically equivalent.

Preparations of St Johns Wort are widely available, and patients may be taking it without the prescriber's knowledge. Co-administration with many commonly prescribed psychotropic agents is potentially hazardous.

According to NICE (CG90):
“St John’s Wort is more effective than placebo on achieving response in both moderate and severe depression, and on reducing depression symptoms in moderate depression. There appears to be no difference between St John’s Wort and other antidepressants, other than in moderate depression where it is better at achieving response and in severe depression where it is less effective than low dose antidepressants in achieving response. However, St John’s Wort appears as acceptable as placebo, and more acceptable than antidepressants, particularly TCAs, with fewer people leaving treatment early due to side effects and reporting adverse events.”

Many trials on SJW are flawed in terms of inadequate trial period, variability of preparations used, heterogeneity of patients included and sub-therapeutic control drug dosing.

SJW must not be used or recommended for use in children and young people (≤18yrs old). If such a patient is taking this preparation, they must be informed of the risks:

- There are no trials in children and young people upon which a clinical decision could be made
- Unknown side effect profile
- Known drug interactions (including contraceptives)
- Unknown quantity of active ingredient in the different preparations available.

Young patients taking this preparation should be advised to discontinue treatment (gradually and preferably under supervision), be monitored for recurrence of...
depression or assessed for alternative treatments in line with the recommendations within NICE Clinical Guidance 28.

**Side-effects:**
- gastro-intestinal irritation (nausea, constipation)
- dizziness
- headache
- fatigue
- dry mouth
- restlessness

Skin rash and photosensitivity have also been reported. As with other antidepressants, switches in bipolar patients to mania have also been reported.\(^{38}\)

**CSM warnings**

The CSM has advised of important interactions possible between SJW and prescribed medication.\(^{39}\) Evidence suggests that SJW can induce drug metabolising enzymes and lower levels of drugs such as warfarin, oral contraceptives, digoxin, ciclosporin, indinavir and theophylline. These combinations should be avoided as treatment failures have been reported. SJW may also interact with some antiepileptic drugs such as carbamazepine.

The possibility of serotonin syndrome exists with any serotonergic agent so all antidepressants have the potential for drug interaction, but particularly SSRIs and triptans (for migraine treatment). SJW should not be taken with any drugs with significant serotonergic action.

**NICE Recommendation**\(^1\)

Although there is evidence that St John’s Wort may be of benefit in mild or moderate depression, practitioners should:

- not prescribe or advise its use 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 drugs (including oral contraceptives, anticoagulants and anticonvulsants
Interactions of SSRIs with other medication

The following table has been taken from NICE Clinical Guideline 91.

<table>
<thead>
<tr>
<th>Medication for chronic physical health problem</th>
<th>Recommended antidepressant(s)</th>
</tr>
</thead>
</table>
| Non-steroidal anti-inflammatory drugs (NSAIDs) | • Do not normally offer SSRIs – but if no suitable alternatives can be identified, offer gastroprotective medicines (e.g. proton pump inhibitors) together with the SSRI  
  • Consider mianserin, mirtazapine, moclobemide, reboxetine or trazodone |
| Warfarin and heparin | • Do not normally offer SSRIs  
  • Consider mirtazapine (note that when taken with warfarin, the INR (International Normalised Ratio) may increase slightly) |
| Aspirin | • Use SSRIs with caution – if no suitable alternatives can be identified, offer gastroprotective medicines together with the SSRI  
  • When aspirin is used as a single agent, consider trazodone, mianserin or reboxetine  
  • Consider mirtazapine |
| “Triptan” drugs for migraine | • Do not offer SSRIs  
  • Offer mirtazapine, trazodone, mianserin or reboxetine |
| MAO-B inhibitors (for example selegiline and rasagiline) | • Do not normally offer SSRIs  
  • Offer mirtazapine, trazodone, mianserin or reboxetine |
| Theophylline, clozapine, methadone or tizamidine | • Do not normally offer fluvoxamine  
  • Offer sertraline or citalopram |
| Flecaainide or propafenone | • Offer sertraline as the preferred antidepressant  
  • Mirtazapine and moclobemide may also be used |
| Atomoxetine | • Do not offer fluoxetine or Paroxetine  
  • Offer a different SSRI |
SSRIs – licensed Indications

The following table shows the current licensed indications for each SSRI, as detailed in their Summary of Product Characteristics:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Depression</th>
<th>PD</th>
<th>OCD</th>
<th>PTSD</th>
<th>Social Phobia</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Yes</td>
<td>Yes – with or without agoraphobia</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Yes</td>
<td>Yes – with or without agoraphobia</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Generalised anxiety disorder</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Yes (aged 8 years and over - see SPC)</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Bulimia Nervosa</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Yes-with or without anxiety</td>
<td>Yes – with or without agoraphobia</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Generalised anxiety disorder</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Yes</td>
<td>Yes – with or without agoraphobia</td>
<td>Yes (aged 6 years and over)</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

PD = panic disorder  
OCD = obsessive compulsive disorder  
PTSD = post traumatic stress disorder
Using Antidepressants in Children and Young People\(^{17}\)

Antidepressant therapy should only be offered in combination with a concurrent psychological therapy. If such therapy is declined, then medication may still be given provided there is regular monitoring and follow up of adverse drug reactions.

Medication may only be prescribed after assessment and diagnosis by a child and adolescent psychiatrist.

Fluoxetine is the only antidepressant for which trials show that benefits outweigh risk, and should be prescribed first line. The starting dose should be 10mg daily, increased if necessary to 20mg daily after a week. Consider lower doses for children of lower body weight.

Second line options are citalopram and sertraline, with the following considerations:

- patient and parent/carer(s) have been fully involved in discussions of benefits and risks
- patient and parent/carer(s) have been given appropriate written information about the rationale for drug treatment, delay in onset of effect, time course of treatment, possible side effects, need to take medication regularly as prescribed, etc
- depression is sufficiently severe and/or causing sufficient serious symptoms to justify trying another antidepressant
- there is evidence that fluoxetine plus psychological therapy have been given a fair trial
- there has been a reassessment of the patient to check the likely causes of the depression and the resistance to treatment
- advice has been sought from a senior/consultant child and adolescent psychiatrist
- the child/young person and their parent/guardian have both signed an appropriate and valid consent form

There is little evidence regarding the effectiveness of upper daily adult doses in children and young adults, but these may be considered in older children of higher body weight and/or when in severe illness, an early clinical response is important.

Arrange to monitor adverse drug reactions – e.g. weekly for the first 4 weeks of treatment, and record in notes. Check for suicidal behaviour/self-harm/hostility at the beginning of treatment. Use a recognised self-reporting scale where appropriate.

Consider possible interactions with other drugs (including recreational), alcohol and complementary/alternative therapies.
Antidepressants in Pregnancy

We would like to acknowledge the work done by OBMH pharmacy on this section.

Depression affects between 12 and 20% of pregnant women, with 2 to 13% of women requiring antidepressant treatment. Major depression during pregnancy is a risk factor for the development of postpartum depression which could lead to a recurrent depressive illness. Psychiatric disorders contribute to 12% of all maternal deaths, with suicide being identified as the leading cause of maternal mortality in the UK. With any pregnancy, there is a background rate of 2 - 4% for malformations. Untreated depression is not only a risk for the mother, but it also carries a risk for the developing foetus and the newborn child.

Depression during pregnancy may impair the neurocognitive and socioemotional development of the child, result in preterm birth, predict sleep problems in infancy and toddlerhood, alter neuroendocrine function, and increase the risks of mental and medical disorders in the offspring in later life.

The first trimester is generally considered the most sensitive time for abnormalities to occur. The magnitude of risks of malformation associated with most psychotropic medications are not reliably established. The potential harm of treatment must continually be balanced against the risks posed to the woman and infant by the illness. It is the clinician’s responsibility to support the woman in reaching decisions. In circumstances where this is not possible, the clinician will have to take responsibility for guiding the woman, taking full account of the circumstances and any existing advance decisions she may have made.

Tricyclic antidepressants

TCAs are generally considered to be the first line antidepressants for use during pregnancy. This is based on the length of time that they have been in use and the cumulative safety data that indicates that this class of drug is not associated with an increased incidence of birth defects above the background rate of 2-4%.

The TCAs with the greatest amount of accumulated safety data are amitriptyline, desipramine, imipramine and nortriptyline and these are therefore preferred, if possible. There are less data with other TCAs but they are generally all classed together as being suitable in pregnancy (but see note below regarding clomipramine).

Clomipramine – a note

A report made in 2006 noted an increased risk for cardiovascular defects after maternal use of clomipramine during pregnancy. The report cites an association between clomipramine and cardiac malformations and quotes an odds ratio of 1.87 (95% CI 1.16 - 2.99). The malformations were mainly ventricular and atrial septal defects. Authors citing this report suggest that further studies are needed to confirm this finding. The report is from a Swedish registry and due to the nature of the reporting to the registry (a registry of this nature is more likely to receive reports of malformations than reports of no malformation with drug use during pregnancy), it is possible that the results may be biased towards finding a risk. Other studies have
found no association with cardiac malformations or any other malformations with clomipramine. The mechanism of action of clomipramine is predominantly via serotonin reuptake inhibition, and in view of the recent new information relating to the SSRIs please also refer to the section on SSRIs (below) when considering the use of clomipramine in pregnancy.

Changes in TCA efficacy
Altered pharmacokinetics, particularly during the second and third trimester, may lead to a sub-therapeutic response. Patients should be closely monitored and doses adjusted accordingly. Please contact MI if more information is required.

Neonatal discontinuation symptoms
All antidepressants can cause discontinuation symptoms in the newborn – see box 1 for further information.

### Box 1. Withdrawal symptoms in the neonate

Short term neonatal withdrawal symptoms have been reported with all antidepressants. Symptoms include jitteriness, shivering, tremors, increased muscle tone, feeding and sleep disturbances, irritability, agitation, respiratory distress and excessive crying. Symptoms are usually mild and transient, but may need treatment in a special care unit. Rarely, neonatal convulsions have occurred.

The antidepressants with shorter half-lives, such as paroxetine or venlafaxine are considered to be more likely to cause these problems. There have been case reports of neonatal convulsions after late in utero exposure to paroxetine. It has been suggested that the poor metaboliser genotype of CYP2D6 may be a risk factor for perinatal complications in infants exposed to SSRIs late in pregnancy.

It might be possible to avoid these withdrawal effects by tapering the antidepressants during the third trimester or even stopping completely immediately prior to delivery. However consideration should be given to the high risk of relapse on stopping treatment at this vulnerable stage and the antidepressant should be restarted immediately after delivery at the pre-pregnancy dosage.

Pros and cons of using TCAs
The SSRIs are the most frequently prescribed antidepressant in the general population due to the greater burden of side effects associated with the TCAs, which include their toxicity in overdose. Therefore when considering the choice of antidepressant in pregnancy, side effect potential should be taken into account. TCAs should not be prescribed in mothers at risk of overdose. TCA toxicity not only poses a serious risk to the mother but can also result in foetal harm. The indication for the antidepressant may also affect the choice. For example TCAs are usually avoided in patients with bipolar disorder due to the risk of precipitating a manic switch, and SSRIs are more effective than TCAs in OCD and other anxiety disorders.
Long-term effects

The long-term neurodevelopmental effects of antidepressants has not been extensively studied. However, a small study of 80 preschool children found that in utero exposure to TCAs did not affect their neurodevelopment (cognitive, language and behavioural development). 49,50

Selective Serotonin Reuptake Inhibitors (SSRIs) in pregnancy

Many SSRIs are used in pregnancy because they are so frequently prescribed to women of child bearing age, who become pregnant while taking them. Experience with them is therefore growing, but remains still far smaller than with the TCAs.

Cardiac malformations

In March 2010, the Medicines and Healthcare products Regulatory Agency (MHRA) issued a safety bulletin that highlighted a possible link between the use of fluoxetine and a small increase in the risk of cardiac malformations (specifically septal heart defects) that may be similar to the risk highlighted with paroxetine. Analysis of data from 5 cohort studies gave an odds ratio of 1.43 (95% CI 0.83–2.47) for congenital cardiac defects. The background rate of cardiac malformations in the general population is 1 in 100 and this possible increase in risk may translate to 2 in 100 pregnancies. Although the mechanism is not known, it is possible that the risk is a class-effect with SSRIs.

Prior to March 2010 the SSRIs were not considered to be associated with an increase in incidence of malformations above the background rate of 2-4%, with the exception of paroxetine which was highlighted in 2005 as possibly causing a small increase in the risk of cardiac malformations. Fluoxetine was being recommended by the National Teratology Information Service (NTIS) as the SSRI of choice, based on the accumulated safety data associated with this SSRI. Often if patients were stable on other SSRIs, the recommendation was for those patients to remain on what was keeping them well, particularly as there was a growing amount of safety data with citalopram and sertraline, with one author suggesting that these SSRIs may have a better average safety profile in pregnancy than fluoxetine. 49

Other conflicting research has been published in the literature, but this has not been highlighted by the MHRA specifically. A population based cohort study conducted in Denmark suggests an increased risk of cardiac defects associated with SSRIs, in particular sertraline and citalopram. 52 However, another retrospective cohort study found no association between SSRI use during pregnancy and congenital heart defects. 53 Authors of a paper published in 2008 collected data on exposures to paroxetine during the first trimester of pregnancy from international teratology information services and from authors of database studies. The data represented a very large number of exposures (>3000) and indicated that the incidence of cardiac defects was no different to the expected incidence in the general population. 54 This contrasts findings from a meta-analysis published in 2007 that investigated whether first trimester exposure to paroxetine was associated with an increased risk of congenital malformations. 55 The authors concluded that there was a significant increase in the risk of cardiac malformations however a Centre for Reviews and Dissemination (DARE) assessment of this meta-analysis felt that the reliability of the
conclusion was unclear because insufficient details of the included studies were provided. Unfortunately there are various limitations within all of the currently available studies and data sets, leaving the question of whether there truly is a specific risk of cardiac malformations with the SSRIs unanswered. Detecting small increases in congenital malformations as a result of medication use is difficult without conducting sufficiently powered well-designed prospective studies. The NTIS confirm that a causative risk for cardiac malformations has not been established for any SSRI however in view of the possible association they now advise that there are no recommendations for a specific SSRI of choice in pregnancy.

In summary – cardiac malformations
The SSRIs may be associated with a small increase in the risk of congenital heart defects. The MHRA has highlighted this risk for two SSRIs – paroxetine and fluoxetine. However it is possible that this is a class effect because the more commonly used SSRIs have all been implicated in at least one published study, making it difficult to conclude that one SSRI is safer than another. If there is a risk, the information that currently exists indicates that the absolute risk is very low; an increase in the incidence of cardiac malformations from 1 in 100 to about 2 in 100 following first trimester exposure. Clinicians and patients need to balance the small risks associated with SSRIs (see also below for other risks with SSRIs) against those associated with under-treatment or no treatment of depression during pregnancy.

Persistent Pulmonary Hypertension of the newborn (PPHN)
PPHN is rare but is associated with significant morbidity and mortality. It occurs in an estimated 1 or 2 per 1000 live births. A small cohort study conducted in 1999 found that 2 of 73 infants exposed to fluoxetine in late pregnancy had PPHN as compared with none of the 101 exposed only in early pregnancy. Data from a retrospective case-control study by the same author in 2006 also observed an association between the maternal use of SSRIs in late pregnancy and PPHN in the offspring. This study included 377 infants with PPH compared with 836 matched control infants. Although there was no association of PPHN with maternal exposure to SSRIs before the 20th week of gestation or with exposure to non-SSRI antidepressants at any time in pregnancy, a significant association was found with the use of SSRIs after 20 weeks of gestation (adjusted odds ratio for SSRI use after the 20th week of gestation relative to no use in the pregnancy 6.1; 95% CI: 2.2 to 16.8). Based on the above study (making the assumption that there is a causal relationship), the risk equates to about 6 to 12 per 1000 births or, alternatively, that 99 percent of women exposed to one of these medications late in pregnancy will deliver an infant unaffected by PPHN. An epidemiological study published in 2008 aimed to verify the observation of an association between maternal SSRI use and PPHN using a Swedish medical birth register. An association between maternal SSRI use and PPHN in births after 34 weeks of gestation carried a risk ratio of 2.4 (95%CI 1.2 to 4.3) based on women who reported SSRI use in early pregnancy. From a subgroup who also had prescriptions for an SSRI from antenatal care later in pregnancy, the risk estimate
was 3.6 (1.2 to 8.3). Based on all the above data, the MHRA recently issued advice to professionals that SSRIs increase the risk of PPHN. The MHRA state that the observed increase in risk is about an extra 3–4 cases of PPHN per 1000 pregnancies. The MHRA also advise that due to the related mechanism of action, a potential risk with the Serotonin & Noradrenaline Reuptake Inhibitors (SNRIs) cannot be ruled out.

**Neonatal discontinuation symptoms**
All antidepressants can cause discontinuation symptoms – see box 1 for further information.

**Adaptation problems**
Some studies have suggested that SSRI exposure in the third trimester may be related to perinatal complications, such as poor neonatal adaption, cyanosis on feeding and jitteriness. It has not been firmly established whether these neurobehavioural disruptions are related to drug toxicity in the neonate or to a discontinuation syndrome. In most cases the effects are mild and self limiting and infants are managed with supportive care.

**Bleeding disorders**
Bleeding disorders and haematomas have been associated with the use of SSRIs in adults. Gestational exposure to SSRIs has been shown to reduce platelet serotonin uptake in the foetus and there are a handful of cases of haemorrhage in newborns reported in the literature.

**Long-term effects**
The long-term neurodevelopmental effects of antidepressants has not been extensively studied. However several small studies indicate that neurobehavioural, cognitive, and language development in infants and children born to mothers who took fluoxetine and other SSRIs during pregnancy were similar to that of non-exposed children. In two of the studies a slight delay in motor development and motor control was observed.

**Monoamine Oxidase Inhibitors (MAOIs) in pregnancy**
MAOIs are generally not recommended for use during pregnancy. They have been associated with a high incidence of toxicity in humans and the possible interaction with tyramine from certain foods may cause an acute hypertensive crisis. In addition, MAOIs can exacerbate pregnancy associated hypertension, which can lead to alterations in placental blood flow and in turn affect foetal growth and development. There is conflicting evidence about the association of MAOIs with congenital malformations. A small number of studies and case reports have suggested an increased incidence of congenital malformations with phenelzine and tranylcypromine, however the number of cases is so small that a causal relationship cannot be confirmed. Data on the use of isocarboxazid in pregnancy is very limited and there is no information on the use of moclobemide in pregnancy.

If a mother discovers she is pregnant while taking an MAOI she should discuss the possibility of switching to an alternative agent, taking into account risk of destabilising her mental state with any switch. Exposure to MAOIs is not an indication for termination of a pregnancy and a detailed foetal scan can be
recommended to reassure patients. As with other antidepressants, withdrawal symptoms in the neonate may occur (see box 1 for further information).

Other antidepressants in pregnancy
Unfortunately with the newer antidepressants such as venlafaxine, mirtazapine, duloxetine, reboxetine and trazodone, the available safety data is relatively limited. So when selecting a treatment for a pregnant woman these antidepressants should be avoided if possible. However, use of these medicines in the first trimester is not an indication for termination. A risk/benefit assessment for any one of these medicines should be carried out. However, it is often deemed appropriate for a woman who is stable on one of these antidepressants to remain on the treatment that is keeping her well, particularly if there is a significant risk of relapse if the treatment were to be changed.

Serotonin & Noradrenaline Reuptake Inhibitors (SNRIs)

- **Venlafaxine:** The limited data available with venlafaxine (in the region of 300 exposed pregnancies) does not indicate a substantial increase in the risk of malformations above the background rate, but see box 2 and notes below. In addition the NICE guideline on antenatal and postnatal mental health advises that prescribers also consider the following risks: high blood pressure at high doses, a higher toxicity index in overdose than SSRIs and some TCAs, and increased risk of neonatal discontinuation (due to the short half-life) – see box 1.

- **Duloxetine:** There is insufficient experience with this new drug to make any conclusions about its safety in pregnancy. Studies in animals have shown reproductive toxicity at systemic exposure levels of duloxetine lower than the maximum clinical exposure. The potential risk in humans is unknown. Venlafaxine and duloxetine inhibit the reuptake of both noradrenaline and serotonin. However venlafaxine is predominantly a serotonin reuptake inhibitor at doses of 150mg or less. The increased cardiac risk for the SSRIs could also apply to SNRIs (see section on SSRIs above). The exact causal relationship and possible mechanism for this effect is unknown so it is impossible to draw any specific parallels between venlafaxine, duloxetine and the SSRIs with the limited data available. Similarly, the increased risk of PPHN associated with SSRI use in late pregnancy could also apply to the SNRIs. There is currently no evidence for an association however, due to the related mechanism of action, a potential risk cannot be ruled out (see SSRIs above).

Presynaptic alpha-2 antagonists

**Mirtazapine:** The limited data available with mirtazapine (in the region of 200 exposed pregnancies) does not indicate a substantial increase in the risk of malformations above the background rate, but see box 2. A prospective study comparing 104 mirtazapine patients to two control groups (one with depressed pregnant women treated with other antidepressants and the other with healthy pregnant women) found that mirtazapine does not increase the risk of major malformations above the baseline rate. In this study both the mirtazapine and the

---

**Box 2. Detecting drug-induced malformations**

It is thought that at least 800 pregnancies would have to be examined to detect a two fold increase in major malformations, and many thousands would be needed to pick up a rare defect that a medicine might cause.
other antidepressant group showed a higher rate of spontaneous abortion and preterm births compared to the healthy pregnant mothers on no medication. This finding has been observed in other studies and may be attributed to the depressive illness rather than the medication. Several authors have described cases where mirtazapine has been used to treat hyperemesis gravidarum in pregnancy with depression.

Selective Noradrenaline Reuptake Inhibitors

**Reboxetine:** No clinical trial data on exposure to reboxetine during pregnancy are available. However, postmarketing safety data on a very limited number of exposed pregnancies indicate no adverse effects of reboxetine on pregnancy or on the health of the foetus/newborn child, but see box 2. Animal studies in general do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development or parturition. Some impairment of growth and development has been noted in rat neonates. Reboxetine should only be used in pregnancy if the potential benefits of treatment to the mother outweigh the possible risks to the developing foetus.

TCA-related antidepressants

**Trazodone:** The limited data regarding trazodone use during pregnancy do not indicate a substantial increase in the risk of malformations, but see box 2. No indication of teratogenicity was observed in approximately 70 pregnancies where patients were exposed to trazodone in the first trimester of pregnancy. Data from a surveillance study of 112 women exposed to trazodone in the first trimester did not show an increase in congenital malformations. In addition, the results of a multicentre prospective study that compared women exposed to trazodone (n=58) or nefazadone (n=89) with 2 other groups of women (one exposed to other antidepressants (n=147) and one to non-teratogenic medicines (n=147)) found no statistically significant differences in endpoints (rates of major malformations, spontaneous or therapeutic abortions, and premature labour, and birth weight).

**Melatonin-receptor agonist and selective serotonin receptor antagonists**

**Agomelatine**

There are no clinical data regarding exposure to agomelatine during pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

For further advice, or to discuss an individual case please contact MI.
Antidepressants in breastfeeding

We would like to acknowledge the work done by OBMH pharmacy on this section.

Drug treatment of depression in a breastfeeding mother can pose a clinical dilemma since the needs of both mother and infant must be balanced. When an antidepressant is indicated, with careful selection of agent and dosage regimen, it is seldom necessary to deny the healthy infant the known benefits of breastfeeding. A decision to treat a breastfeeding mother with antidepressants should involve a case-by-case assessment of the risk:benefit ratio. Monotherapy is recommended and the infant should be carefully monitored for sedation, respiratory depression, weight gain and developmental milestones.

Premature infants (babies born before 37 weeks of gestation) should not be exposed to psychotropic drugs via breast milk as reduced excretory functions may lead to drug accumulation on prolonged exposure and such infants may also be more sensitive to the effects of CNS agents. If a mother wishes and is able to express, there is the possibility that breastfeeding could begin once the infant is a number of weeks older, however as every premature infant is different it would be hazardous to make specific recommendations for this situation. The current recommendation for this scenario is to contact a specialist for advice on a case by case basis.

In addition, infants of very low birth weight or with medical problems of their own should not be exposed to medication through the breast milk.

Little is known about the physical or mental development of infants exposed to antidepressants via breast milk. A study in 2005 monitored maternal mood and infant weight at 6, 12 and 18 months in a group of 78 breastfeeding women taking antidepressants, including citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine plus additional unspecified TCAs in some cases. Infant weights at 6 months did not differ significantly from the normal population. However, infants of mothers who experienced longer depressive episodes (2 months or more) following delivery weighed significantly less compared with infants whose mothers had only brief depressive episodes or infants whose mothers had no depressive episodes in the post partum period. This finding was also demonstrated when medication dose and infant birth weight were included as covariates. The study suggests that postnatal depression may influence behaviours that may affect infant weight gain.

**TCAs**

All TCAs are excreted in the breast-milk in small amounts, though data on the passage of TCAs into milk are limited. All TCAs (except doxepin) can be given to women who are breastfeeding provided the infant is full term, healthy and can be monitored for his/her progress. The ideal TCA for use in breastfeeding is non-sedating with a shorter half-life, reduced anticholinergic effects, no active metabolites, high protein binding and for which clinical data are available. TCAs most closely meeting these criteria are imipramine and nortriptyline and these are therefore preferred when clinically appropriate. Lofepramine has a lower potential for anticholinergic effects, but no quantitative studies have been conducted.

Amitriptyline, clomipramine, desipramine and dosulepin are more sedating so the infant should be monitored carefully for drowsiness if these are prescribed. A handful of case reports have documented adverse effects in infants exposed to doxepin through breastfeeding, so this should be avoided. Risks can further be minimised by
using a single daily dose of a TCA and breastfeeding immediately before drug administration. For very young infants feeding frequently, an option to consider is to substitute one feed with one bottle feed in order to avoid drug peak levels at about 1-3 hours post dose. Use of other sedating agents in the mother should be avoided since sedation can be additive. Infants should be monitored for drowsiness or other behavioural changes.

**SSRIs**

All SSRIs have been detected in breast milk in small amounts and although data is still relatively limited the SSRIs are the group of antidepressants for which the most data exist to support their use during breast-feeding. Paroxetine or sertraline are the preferred SSRIs for use in breast-feeding mothers due to their short half-lives, the lower passage into milk and greater amounts of safety data compared with other SSRIs. Fluoxetine, citalopram and escitalopram have the longest half-lives of this group and if an SSRI is considered essential and is being selected for use in a mother who is breastfeeding, these are best avoided on current evidence, particularly in neonates where reduced excretory function may prolong the drug half-life further and increase the risk of adverse effects. However, if a woman has been successfully treated with one of these SSRIs during pregnancy and needs to continue therapy after delivery, there is usually no need to change the drug, provided the infant is full term, healthy and can be adequately monitored. All SSRIs should be used for the shortest possible time and at the lowest effective dose. Adverse effects associated with infant exposure to SSRIs in breast milk have been reported for citalopram, fluoxetine, paroxetine, sertraline, and escitalopram therefore all infants exposed to SSRIs via breast milk should be monitored for adverse effects such as sedation, poor feeding and behavioural effects. Long-term SSRI exposure to the infant should be avoided where possible due to the limited evidence and experience relating to their effects on development. However, the limited data available regarding the effects of SSRI exposure via breast-milk on weight gain and infant development are encouraging.

**Other antidepressants**

Experience of the use of MAOIs, moclobemide, reboxetine, venlafaxine, mirtazapine and duloxetine in lactation is very limited and they are not considered as first line antidepressants in breastfeeding women. Due to the complete absence of data with first generation MAOIs and their potential to cause serious interactions with some food and drugs, a decision whether to discontinue the drug or not to breast-feed should be made.

For further advice, or to discuss an individual case please contact MI.
References

1. NICE Clinical Guideline 90 Depression: Treatment and management of depression in adults. October 2009
7. www.mhra.gov.uk
12. NHS Northern & Yorkshire Regional Drug & Therapeutics Centre (The National Teratology Information Service). Summary on Antidepressant use in pregnancy. February 1999
13. What is the optimal management of depression in a breastfeeding mother? UK Medicines Information Website – FAQ 20
16. Committee on Safety of Medicines. Use of Selective serotonin reuptake inhibitors (SSRIs) in children and adolescents with major depressive disorder (MDD) 2003
22. Nurnberg HG et al. Sildenafil treatment of women with antidepressant-associated sexual dysfunction: a randomized controlled trial. JAMA 2008;300:395-404
Antidepressant Guidelines

47. Parry BL. Assessing risk and benefit: to treat or not to treat major depression during pregnancy with antidepressant medication. Am J Psych 2009;166(5):512-514
56. Personal communication with the National Teratology Information Service, UKMI Specialist Centre for Medicines in Pregnancy, Newcastle 15th April 2010.
57. Chambers C. Selective serotonin reuptake inhibitors and congenital malformations – the small risk of harm must be balanced against risk of suboptimal or no treatment. BMJ 2009;339:703-704
62. Personal communication with the National Teratolgy Information Service, UKMI Specialist Centre for Medicines in Pregnancy, Newcastle 26th November 2009.
63. Eli Lilly & Co. Cymbalta (duloxetine) Summary of Product Characteristics. Date of revision of the text: 20 November 2009
69. UKMI Medicines Q&As. Management of depression in breastfeeding mothers – are tricyclic antidepressants safe? Q&A 251.1, expiry 16 February 2011
70. UKMI Medicines Q&As. Management of depression in breastfeeding mothers – are selective serotonin reuptake inhibitors (SSRIs) safe? Q&A 252.1, expiry 12 March 2011
71. UKMI Medicines Q&As. Management of depression in breastfeeding mothers – are reboxetine, venlafaxine, duloxetine, mirtazapine and MAOIs safe? Q&A 253.1, expiry 20 March 2011