ANTIDEPRESSANT GUIDELINES

TREATMENT OF DEPRESSION
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Acknowledgements:

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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

**Medicines Formulary**
- Treatment Choices: 4
- Treatment Algorithm: 6
- Factors Affecting Choice: 8
- General Treatment Principles: 10

**Additional Information/Guidance**
- Clinical Information: 11
- Treatment Options for Special Populations: 12
- Antidepressant-Induced Sexual Dysfunction: 13
- Hyponatraemia: 14
- Serotonin Syndrome: 14
- Switching & Stopping: 15
- Treatment Resistance: 17
- St John's Wort: 20
- SSRIs – licensed indications: 22
- Using Antidepressants in Children and Young People: 23

References: 24
Antidepressant Guidelines

MEDICINES FORMULARY

ANTIDEPRESSANTS

FIRST LINE TREATMENT CHOICES

- sertraline

other generic SSRIs
- citalopram
- fluoxetine
- paroxetine

ALTERNATIVE FIRST LINE CHOICE
(where an SSRI is not appropriate)

- mirtazapine

SECOND LINE CHOICES

- mirtazapine
- venlafaxine

tricyclic antidepressants (TCA) – (lofepramine preferred)
- moclobemide
- reboxetine

Other TCAs – amitriptyline, imipramine, clomipramine, trimipramine

FOR SECONDARY CARE INITIATION ONLY

- phenelzine
- tranylcypromine
- tryptophan

Antidepressant combinations
Augmentation Strategies

Antidepressants not approved by BHFT:

- Escitalopram (Cipralex®)*
- Agomelatine

*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>1st</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd</td>
<td></td>
<td></td>
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<tr>
<td>3rd</td>
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<tr>
<td>4th</td>
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<td></td>
<td></td>
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<tr>
<td>5th</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>6th</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.information@berkshire.nhs.uk
Antidepressant Guidelines

**Depression – Drug Treatment Algorithm**

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.

- **Start antidepressant** and titrate (if necessary) to therapeutic dose. Assess** after 2 weeks
  - **Review after 3-4 weeks**
  - **No / Minimal improvement**
  - **Some improvement**

- **Increase support Consider dose increase in line with SPC if tolerated**
  - **Side effect (s/e) or person prefers**

- **Continue for further 2-4 weeks**
  - **Effective tolerated**
  - **Still ineffective or s/e or person prefers**

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

- **Not tolerated**
  - **Ineffective**
  - **Check compliance**
  - **Review diagnosis including possibility of additional physical or psychiatric diagnoses requiring treatment**
  - **Refer to suggested treatments for treatment refractory depression**

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

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* Discuss choice of drug with the patient regarding adverse effects, therapeutic effects, discontinuation effects etc
** Assess after 1 week for those at risk of suicide or age under 30, and then frequently as necessary
At each review assess response, adherence to drug treatment, side effects, suicide risk
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.

*** 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 6.0 March 2010
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

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**Notes:**

- 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.

- Only for depression where the person also has a chronic physical health problem and associated functional impairment

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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/IIs 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

- 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 (equivalent to 150mg daily of a tricyclic antidepressant)
  - 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 recognize 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>Anti-cholinergic</th>
<th>Cardiac</th>
<th>Nausea</th>
<th>Sedation</th>
<th>Toxicity in Overdose</th>
<th>Pro-convulsant 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>0</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>
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<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Phenelzine</td>
<td>1.5</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>2.5</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Others</strong></td>
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<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>+</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>
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<td>0</td>
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<td>+</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>


**Key:**

- +++ significant effect
- ++ moderate effect
- + mild effect
- 0 little or minimal effect
- ? no information or little reported
- * has active metabolite with prolonged half-lives
# Treatment of Special Patient Populations

<table>
<thead>
<tr>
<th>Condition/Population</th>
<th>1st Choice</th>
<th>Alternative/2nd Choice</th>
<th>Avoid</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pregnancy</strong></td>
<td>imipramine</td>
<td>SSRIs (N.B. Paroxetine may be less safe)</td>
<td>few data available. Please consult (MI) for specific information</td>
<td></td>
</tr>
<tr>
<td>Lactation</td>
<td>imipramine</td>
<td>doxepin</td>
<td>minimal data available. Consult MI for specific info</td>
<td></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><strong>Epilepsy</strong></td>
<td>SSRIs mirtazapine</td>
<td>tricyclics</td>
<td>consult pharmacy for details of interactions with anti-epileptic drugs <em>important</em> Very limited data and experience with newer agents</td>
<td></td>
</tr>
<tr>
<td><strong>Liver disease</strong></td>
<td>paroxetine</td>
<td>citalopram sedative tricyclics MAOIs</td>
<td>dosage reduction often required. Other agents may be possible. Consult MI for advice.</td>
<td></td>
</tr>
<tr>
<td>Renal impairment</td>
<td>citalopram mirtazapine</td>
<td></td>
<td>dosage reduction may be required. Low dose tricyclics may be possible. Consult MI for advice.</td>
<td></td>
</tr>
<tr>
<td>Adolescence</td>
<td>fluoxetine</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>
<td></td>
</tr>
<tr>
<td><strong>Old age</strong></td>
<td>SSRIs moclobemide</td>
<td>venlafaxine tricyclics (generally)</td>
<td>Changes in absorption, distribution, metabolism and excretion- adverse effects more likely.- start low, go slow; monitor effects</td>
<td></td>
</tr>
</tbody>
</table>

10,11,12,13,14,15,16,17,40
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”

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 risk 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.

Sternbach’s Diagnostic Criteria:

- 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 presentation; 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:

- 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.\(^{27}\) Symptoms may also be mistaken for a relapse of illness or the emergence of a new physical illness, leading to unnecessary interventions.\(^ {28}\)

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)\(^ {11}\)
- 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\(^ {28}\) in those prescribed short half-life drugs,\(^ {29}\) 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</td>
<td>“flu”-like symptoms</td>
<td></td>
</tr>
<tr>
<td>irritability</td>
<td>(chills, myalgia, excessive sweating, headache, nausea)</td>
<td>“shock-like” sensations</td>
<td></td>
</tr>
<tr>
<td>ataxia</td>
<td>insomnia</td>
<td>(exacerbated by movement)</td>
<td></td>
</tr>
<tr>
<td>movement disorders</td>
<td>vivid dreams</td>
<td>insomnia</td>
<td></td>
</tr>
<tr>
<td>insomnia</td>
<td>cognitive impairment</td>
<td>excessive dreaming</td>
<td></td>
</tr>
<tr>
<td>somnolence</td>
<td>slowed speech</td>
<td>“flu”-like symptoms</td>
<td></td>
</tr>
<tr>
<td>vivid dreams</td>
<td>pressured speech</td>
<td>“shock-like” sensations</td>
<td></td>
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<td>cognitive impairment</td>
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<td></td>
<td>crying spells</td>
<td></td>
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<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>occasionally</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hallucinations</td>
<td>occupational movement disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>paranoid delusions</td>
<td>mania</td>
<td></td>
<td></td>
</tr>
<tr>
<td>occasional movement disorders</td>
<td>problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mania</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>problems with</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Berkshire Healthcare NHS Foundation Trust
Edition 6.0 March 2010
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,(^{31}) aiming for a level of 0.4-1.0mmol/l</td>
<td>Sound evidence base&lt;br&gt;Effective in around 50% cases&lt;br&gt;Recommended by NICE</td>
<td>Less acceptable to patients&lt;br&gt;Potentially toxic drug requiring plasma level monitoring and specialist initiation</td>
</tr>
<tr>
<td>Add atypical antipsychotic(^{1}) i.e. olanzapine, aripiprazole, risperidone or quetiapine.</td>
<td>Some good evidence e.g. olanzapine/fluoxetine combination, and some RCTs e.g. aripiprazole&lt;br&gt;Usually well tolerated</td>
<td>Developing evidence base&lt;br&gt;Side-effect burden of atypical antidepressant to consider&lt;br&gt;Patients more likely to leave treatment early due to side-effects</td>
</tr>
<tr>
<td>ECT (^{32})</td>
<td>Effective&lt;br&gt;Well-documented in literature</td>
<td>Poor public perception&lt;br&gt;Needs general anaesthetic&lt;br&gt;Specialist referral</td>
</tr>
<tr>
<td>Add tri-iodothyronine (20-50mcg/day) (^{33})</td>
<td>Reasonable support in literature&lt;br&gt;Well tolerated&lt;br&gt;Recent interest following STAR-D trial</td>
<td>Requires monitoring&lt;br&gt;Caution in cardiovascular disease&lt;br&gt;Most evidence is with tricyclics&lt;br&gt;Requires specialist referral&lt;br&gt;Prolonged treatment may lead to hypothyroidism on discontinuation&lt;br&gt;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)(^{1})</td>
<td>Recommended by NICE&lt;br&gt;Generally well-tolerated&lt;br&gt;Gaining more widespread use</td>
<td>More side-effects with combination treatment&lt;br&gt;Most data with mianserin&lt;br&gt;Risk of blood dyscrasias with mianserin&lt;br&gt;Risk of serotonin syndrome</td>
</tr>
</tbody>
</table>
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)</td>
<td>Could be initiated in primary care</td>
<td>Limited evidence Requires blood pressure monitoring</td>
</tr>
<tr>
<td></td>
<td>Well tolerated</td>
<td></td>
</tr>
<tr>
<td>Add pindolol 2.5mg tds - up to 5mg tds</td>
<td>Well tolerated</td>
<td>Uncertainty regarding optimum dose and duration Contradictory results Data mainly relate to acceleration of response</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Add tryptophan 2-3g tds</td>
<td>Use documented widely</td>
<td>Secondary care only. Data relate mainly to tricyclics/MAOIs Weak evidence base</td>
</tr>
<tr>
<td></td>
<td>Well tolerated</td>
<td></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
### 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</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

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.
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