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Approved by (Group): Drugs and Therapeutic Committee

Approved by (Committee): Quality Committee

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<tr>
<td>May 2014</td>
<td>1</td>
<td>New Guidelines</td>
</tr>
<tr>
<td>May 2016</td>
<td>2</td>
<td>Further guidance on medicine interactions and co-morbidities</td>
</tr>
<tr>
<td>Mar 2019</td>
<td>3</td>
<td>Update in the PTSD section</td>
</tr>
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Membership of the policy development/review team: Audrey Coker, Lead Pharmacist for Clinical Services.

Consultation: Dr Gina Waters, Dr Lucinda Donaldson, Practice Based Team

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1 Introduction

These guidelines have been developed to provide clinical staff with clear guidance on prescribing for various anxiety disorders to ensure safe effective care of patients in line with current NICE and national good practice guidance and trust formulary.

2 Aims and objectives

To ensure quality and cost-effective prescribing of medicines and to provide optimal therapy in the treatment of anxiety disorders.

3 Scope of the policy

This policy relates to prescribing in patients with a diagnosis of anxiety disorders (generalised anxiety disorder, panic disorder, obsessive compulsive disorder, post-traumatic stress disorder, body dysmorphic disorder, social phobia and simple phobia).

4 Key points

4.1 First line medicine choice in the treatment of anxiety disorders

<table>
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<th>Table 1:</th>
<th>First-line antidepressants</th>
<th>Type of anxiety disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sertraline</td>
<td>Generalised anxiety disorder.</td>
<td></td>
</tr>
<tr>
<td>SSRI</td>
<td>Panic disorder, obsessive compulsive disorder.</td>
<td></td>
</tr>
<tr>
<td>SSRI or venlafaxine</td>
<td>Social phobia.</td>
<td></td>
</tr>
<tr>
<td>Paroxetine or mirtazapine</td>
<td>Body dysmorphic disorder.</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine.</td>
<td>Post-traumatic stress disorder.</td>
<td></td>
</tr>
</tbody>
</table>
4.2 The choice between psychological and pharmacological treatments should in part be determined by patient choice. Psychological option should always be considered as part of the management plan and should be the intervention of choice in mild conditions.

4.3 An SSRI (serotonin reuptake inhibitor) should be considered for first-line pharmacological treatment, as SSRIs are effective across the anxiety and related disorders, in both the short-term and long-term, and are generally well tolerated (see table 1)¹.

4.4 With all antidepressants, especially SSRIs and venlafaxine, there should be specific discussion and monitoring of possible adverse effects early in treatment (initial worsening of anxiety/agitation, problems sleeping, risk of discontinuation/withdrawal symptoms if the treatment is stopped abruptly or in some instances if a dose is missed or occasionally on reducing the dose). Also, suicidal ideation may rarely occur².

4.5 Treatment response may take up to twelve weeks¹,².

4.6 Antidepressants may cause discontinuation symptoms especially paroxetine and venlafaxine².

4.7 When prescribing SSRIs, be aware of medicine interactions².

4.8 The increased risk of bleeding associated with serotonergic medicines should be taken into account, particularly for older people or people taking other medicines that can damage the gastrointestinal mucosa or interfere with clotting (for example, NSAIDs or aspirin). A prescription for a gastroprotective medicine should be considered in these circumstances².

4.9 Serotonin syndrome particularly with serotonergic medicines and antidepressant medicine combinations should be considered. Symptoms include restlessness, tremor, shivering, myoclonus, confusion and convulsions³.

4.10 Hyponatraemia with antidepressants especially serotonergic medicines should be considered. Symptoms include dizziness, nausea, confusion, malaise, cramps and seizures. Risk factors include older or female patients or some medicine combinations³.

4.11 Patients should be advised that:

- Although antidepressants are not associated with dependence, discontinuation/withdrawal symptoms may occur on stopping or missing doses or occasionally on reducing doses.
- The most commonly experienced discontinuation/withdrawal symptoms are dizziness, numbness and tingling, gastrointestinal, headache, sweating, anxiety and sleep disturbances.
- They should seek medical advice if they experience discontinuation/withdrawal symptoms.
- Patients under 30 years should be warned that these medicines are associated with an increased risk of suicidal thinking and self-harm in a minority of patients².
4.12 The risk of suicidal ideation is thought to be greatest in those <30 years, those with co-morbid depression and those already known to be at higher risk of suicide.

4.13 When stopping antidepressants, the dose should be reduced gradually over an extended period of time (over several weeks to months). If severe discontinuation symptoms occur, reintroducing the antidepressant or prescribing an antidepressant of the same class with a longer half-life should be considered and then the dose gradually reduced.

4.14 Benzodiazepines are not recommended for panic disorder and should be used with care in patients with post-traumatic stress disorder (PTSD). A benzodiazepine for the treatment of generalised anxiety disorder (GAD) in primary or secondary care should not be offered except as a short-term measure during crises. Benzodiazepines should not be routinely offered in patients with social anxiety disorder. Risks of tolerance and dependence limit their use to time adjunctive treatment (up to four weeks). The withdrawal syndrome may develop at any time up to 3 weeks after cessation of a long acting benzodiazepine, or a few hours after cessation of a short-acting one.

4.15 Some benzodiazepines have proven efficacy in panic disorder, GAD and social phobia, but they can cause troublesome sedation in acute treatment, and dependence can occur (especially in predisposed patients) with longer-term use. As they have limited efficacy in relieving depressive symptoms, antidepressants should be preferred in patients with significant comorbid depression. Other than short term treatment, benzodiazepines will be reserved for the treatment of patients already prescribed long-term treatment with benzodiazepines.

4.16 Patients should be advised if the medicines are prescribed off-label. They should be offered patient information leaflets from the 'choice and medication' link on the trust intranet.

4.17 People taking a monoamine oxidase inhibitor should be advised of the dietary and pharmacological restrictions concerning the use of these medicines as set out in the British national formulary.

4.18 The use of cognitive behavioural therapy is outside the scope of this guidance.
5 Generalised anxiety disorder (GAD)

5.1 Medicine choice in the management of generalised anxiety disorder

<table>
<thead>
<tr>
<th>Options</th>
<th>Medicine choice</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line</td>
<td>Sertraline (off-label)</td>
<td>SSRIs may initially exacerbate symptoms. Half the normal starting dose is often required. Higher doses of SSRIs may be associated with greater response rates. Sertraline is the best tolerated.</td>
</tr>
<tr>
<td>Second line</td>
<td>Paroxetine; citalopram (off-label) or fluoxetine (off-label), venlafaxine.</td>
<td>Half the normal starting dose is often required. Higher doses of SSRIs or venlafaxine may be associated with greater response rates. The SSRIs listed are included in the formulary. Fluoxetine is probably the most effective.</td>
</tr>
<tr>
<td>Third line</td>
<td>Pregabalin.</td>
<td>Pregabalin is approved in the trust as a third line option where either two SSRIs or an SSRI and an SNRI have been tried and failed or not tolerated (as per NICE). Pregabalin should not be stopped abruptly as it may precipitate rebound anxiety and seizures.</td>
</tr>
<tr>
<td>Other options</td>
<td>Benzodiazepines-lorazepam, diazepam, clonazepam and clordiazepoxide</td>
<td>Do not offer a benzodiazepine in the treatment of generalised anxiety disorder except as a short-term measure during crises (maximum: two to four weeks). The benzodiazepines listed are included in the trust formulary.</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics</td>
<td>Do not offer in primary care².</td>
</tr>
</tbody>
</table>

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

- Tendency to produce a withdrawal syndrome especially with paroxetine and venlafaxine.
- Side effect profile and potential for medicine interactions.
- The risk of suicide and likelihood of toxicity in overdose (especially with venlafaxine).
- The person's prior experience of treatment with individual medicines especially adherence, effectiveness, side effects, experience of withdrawal syndrome and the person's preference².
- The increased potential risk of suicidality or self-harm in young adults under 30 years when prescribing SSRIs. These patients should be seen within one week of prescribing and monitored for risk of suicidal thinking and self-harm weekly for the first month².

5.3 Before prescribing any medication, the treatment options and any concerns the person has about taking medication should be considered. The reasons for prescribing should be fully explained and information provided on:-

- the likely benefits of different treatments.
- different propensities of each medicine for side effects, withdrawal syndromes and medicine interactions.
- risk of activation with SSRIs and SNRIs with symptoms such as increased anxiety, agitation and problems sleeping.
- gradual development over one week or more of the full anxiolytic effect.
- importance of taking medication as prescribed and the need to continue medicine treatment after remission to avoid relapse².

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5.4 For people who develop side effects soon after starting treatment, the following strategies should be considered:

- Monitoring symptoms closely (if the side effects are mild and acceptable to the patient).
- Reducing the dose of the medicine.
- Stopping the medicine and offering an alternative medicine or a high intensity psychological intervention.

5.5 The effectiveness and side effects of the medicines should be reviewed every two to four weeks during the first three months and then every three months thereafter. Allow twelve weeks to assess if there is any medicine response. Response is usually seen within six weeks and continues to increase over time. If the medicine is effective, the person should be advised to continue taking it for at least a year as the likelihood of relapse is high.

5.6 If a patient’s GAD has not responded to medicine treatment, an alternative medicine or a high intensity psychological interventions should be considered. If a partial response to medication occurred, then a combination with high intensity psychological intervention should be considered. If then a patient has not responded to first and second line treatments, then a referral should be made to secondary care.

5.7 Beta-blockers are not recommended. If a patient is already prescribed a beta-blocker, treatment should be reviewed. An alternative medicine should be considered if necessary. When stopping a beta-blocker, it should be reduced gradually as abrupt withdrawal may precipitate or result in severe exacerbation of angina pectoris, acute myocardial infarction, sudden death, malignant tachycardia, sweating, palpitation and tremor. The specification of product characteristics for propranolol recommends it should be withdrawn over a minimum of ten to fourteen days (although caution should be exercised).

6 Panic disorder

6.1 Medicine choice in the treatment of panic disorder

See table below

<table>
<thead>
<tr>
<th>Options</th>
<th>Medicine choice</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line</td>
<td>Sertraline, citalopram; paroxetine.</td>
<td><strong>Half the normal starting dose is required.</strong> SSRIs may initially exacerbate symptoms. Doses of citalopram and sertraline towards the bottom of the antidepressant range gives the best balance between efficacy and side effects. Higher doses of paroxetine (40mg and above) may be required. Higher doses of all medicines may be effective when standard doses have failed.</td>
</tr>
<tr>
<td>Second line</td>
<td>Clomipramine, Imipramine (off-label).</td>
<td><strong>Half the normal starting dose is required.</strong> Slow titration, suicide risk. Doses of clomipramine towards the bottom of the antidepressant range gives the best balance between efficacy and side effects. Higher</td>
</tr>
</tbody>
</table>
doses of all medicines may be effective when standard doses have failed.

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venlafaxine</td>
<td>Discontinuation symptoms may occur.</td>
</tr>
</tbody>
</table>

6.2 Choice between psychological and pharmacological treatments should in part be determined by patient choice.

6.3 Initial side effects can be minimised by slowly increasing doses\(^1\).

6.4 Antihistamines, antipsychotics or benzodiazepines should not be prescribed for the treatment of panic disorder\(^2\). Beta-blockers are not recommended\(^1\). Patients prescribed these medicines should be reviewed and the medicines stopped if possible. An alternative medicine should be considered if necessary. Refer to section 12 for patients prescribed long-term benzodiazepines. When stopping a beta-blocker, it should be reduced gradually as abrupt withdrawal may precipitate severe exacerbation of angina pectoris, acute myocardial infarction, sudden death, malignant tachycardia, sweating, palpitation and tremor\(^1\). The specification of product characteristics for propranolol recommends it should be withdrawn over a minimum of ten to fourteen days (although caution should be exercised)\(^8\).

6.5 Inform the patient at the time of initiation of potential side effects e.g.

- transient increase in anxiety.
- possible discontinuation symptoms.
- delay in onset of effect.
- time course of treatment.
- the need to take medication as prescribed.
- side effects\(^2\)

6.6 Before prescribing the following should be considered:-

- age.
- previous treatment response.
- risks of deliberate self-harm or accidental overdose (tricyclic antidepressants are more dangerous in overdose than SSRIs).
- tolerability.
- possible interactions with concomitant medications(check appendix 1 of the ‘British national formulary’).
- the person’s preference.
- cost, where equal effectiveness\(^2\).
6.7 Efficacy and side effects should be reviewed within two weeks of starting treatment and again at four, six and twelve weeks\(^2\). Onset of action may be as long as six weeks\(^3\). At the end of twelve weeks, an assessment of the effectiveness of the treatment should be made, and a decision made as to whether to continue or consider an alternative intervention\(^2\).

6.8 Treatment should be reviewed at eight to twelve week intervals if the medicine is continued for more than twelve weeks\(^2\). The optimal duration of treatment is unknown, but should be at least eight months. A large naturalistic study showed convincing evidence of benefit for at least three years. Less than half are likely to remain well after medication is withdrawn\(^3\).

6.9 If there is no response at twelve weeks, a switch to another evidence based treatment should be considered\(^1,2\). If there is no response to an SSRI, a referral should be made to secondary care.

6.10 Treatment can be continued with appropriate monitoring for six months after the optimal dose is reached. The dose can then be tapered\(^2\).

6.11 When stopping, the dose should be reduced gradually over an extended period (three months) to avoid discontinuation reactions\(^1,2\).

6.12 If appropriate, continue care and monitoring\(^2\).

7 Obsessive compulsive disorder (OCD)

7.1 Psychological options should be considered first. Routinely combining medicine and psychological approaches is not recommended for initial treatment\(^2\).

7.2 Medicine choice in the management of obsessive compulsive disorder

See table below

<table>
<thead>
<tr>
<th>Options</th>
<th>Medicine choice</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line</td>
<td>An SSRI e.g. fluoxetine, paroxetine, sertraline or citalopram (off-label).</td>
<td>Anxiolytics may be used cautiously for short periods to counter early activation of SSRIs.</td>
</tr>
<tr>
<td>Second line</td>
<td>Another SSRI or clomipramine.</td>
<td>For patients with a significant cardiovascular risk, an ECG and blood pressure measurement should be carried out before prescribing clomipramine. For people at significant risk of suicide, prescribe small amounts. Monitor the patient regularly until the risk has subsided.</td>
</tr>
<tr>
<td>Treatment resistance</td>
<td>Consider: an antipsychotic added to an SSRI or clomipramine.</td>
<td>If there has not been a response to at least one SSRI alone, combined treatment with CBT and SSRI, a full trial of clomipramine alone, then additional cognitive therapy, adding an antipsychotic to an SSRI, clomipramine or a combination of clomipramine with citalopram should be considered. An ECG, BP and the risk of serotonin syndrome should also be considered.</td>
</tr>
<tr>
<td></td>
<td>Clomipramine combined with citalopram.</td>
<td></td>
</tr>
</tbody>
</table>
7.3 Medication options are listed in table 5.

7.4 Although the doses of SSRIs licensed in OCD are higher than those licensed for the treatment of depression (e.g. fluoxetine 60mg, paroxetine 40-60mg), lower standard antidepressant doses may be effective, particularly maintenance treatment\textsuperscript{3}.

7.5 If there has not been an adequate response to a standard SSRI dose and there are no significant side effects at four to six weeks, a dose increase within the summary of product characteristics should be considered. If a poor response after twelve weeks, another SSRI should be considered\textsuperscript{10}.

7.6 Initial response usually emerges later than in depression (ten to twelve weeks)\textsuperscript{3}. For patients who respond at twelve weeks, treatment should be continued for a further twelve months\textsuperscript{1,8}. If continued beyond twelve months after remission, the need for continued treatment should be regularly reviewed, agreed with the patient and recorded in the notes\textsuperscript{8}. The relapse rate in those who continue treatment for two years is half that of those who stop treatment after initial response (25-40% versus 80\%)\textsuperscript{3}.

7.7 When reducing or stopping SSRI treatment, the dose should be tapered gradually over several weeks, according to the patient's need.

7.8 Take account of the starting dose, medicine half-life and particular profile of adverse effects when determining rate of reduction.

7.9 The patient should be encouraged to seek advice if they experience significant discontinuation/withdrawal symptoms\textsuperscript{9}.

7.10 Antidepressants (excluding SSRIs or clomipramine), anxiolytics or antipsychotic as monotherapy should not normally be used without appropriate co-morbidity. Anxiolytics may be used cautiously for short periods to counter early activation of SSRIs\textsuperscript{10}.

7.11 The addition of an SSRI or clomipramine to psychological treatment should be considered when efficacy needs to be maximised\textsuperscript{2}.

7.12 If a patient fails to respond to an SSRI and psychological treatment, a referral should be made to secondary care.

8 Post-traumatic stress disorder (PTSD)

8.1 Do not routinely offer medicine treatment as the first and only option. The treatment of choice is trauma-focussed therapy. Medication should be offered when patient does not wish to have or cannot engage in therapy\textsuperscript{11}.
8.2 Medicine choice in the management of post-traumatic stress disorder

<table>
<thead>
<tr>
<th>Medicine Choice</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>An SSRI e.g. sertraline;</td>
<td>Consider if a patient has a preference for medicine treatment. Prescribers can make a choice of SSRIs approved in the Trust formulary. Note paroxetine is more likely to be associated with discontinuation symptoms.</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td></td>
</tr>
<tr>
<td>Antipsychotics e.g. risperidone</td>
<td>Consider in addition to psychological therapies to manage symptoms and behaviours e.g. severe hyperarousal or psychotic symptoms and their symptoms have not responded to other medicine or psychological treatments. Evidence is more limited than evidence supporting SSRIs and psychological interventions.</td>
</tr>
</tbody>
</table>

8.3 Adult PTSD sufferers who are at increased risk of suicide and all PTSD sufferers between the 18-29 years should be seen after one week of starting an antidepressant and frequently thereafter until the risk is not considered significant. Adult patients not considered at increased risk of suicide should be seen after two weeks of starting antidepressants and then e.g. every two to four weeks in the first three months and then at greater intervals if the response is good.2

8.4 Lower starting doses are also required.3

8.5 Response is usually seen within eight weeks but can take up to twelve weeks. Allow twelve weeks to assess any medicine response.1 Treatment should be continued for at least six months and probably longer.3

8.6 Signs of akathisia, suicidal ideation, increased anxiety and agitation should be sought, particularly in the initial stages of SSRI treatment. PTSD sufferers should be advised of the risk of these symptoms and to seek help promptly if these are distressing. The use of the medicine should be reviewed if the PTSD sufferer develops marked and/or prolonged akathisia.11

8.7 The dose of antidepressants should be gradually reduced over a four week period (some people may require longer periods). If discontinuation/withdrawal symptoms are mild, reassure the PTSD sufferer and arrange for monitoring. If symptoms are severe, consider re-introducing the original antidepressant (or another with a longer half-life from the same class) and reduce gradually while monitoring symptoms.11

8.8 If there is no response, consider increasing the dose within approved limits.11

8.9 A hypnotic (zopiclone or temazepam) should be considered for sleep disturbance (for short-term use). A suitable antidepressant for longer-term use,
introduced at an early stage to reduce later risk of dependence should be considered.\textsuperscript{11}

8.10 Benzodiazepines should be used with care in patients with PTSD\textsuperscript{3}. Benzodiazepines are associated with specific problems in patients with PTSD: worse overall severity, significantly increased risk of developing PTSD with use after recent trauma, worse psychotherapy outcomes, aggression, depression, and substance use\textsuperscript{21}.

8.11 When a patient responds to medication treatment, the treatment should be continued for at least twelve months, before gradual withdrawal\textsuperscript{11}.

8.12 If there is no response to first line treatment, a referral should be made to secondary care.

8.13 If an antipsychotic is indicated, it should only be prescribed after consultation with a specialist and tolerability considered\textsuperscript{22}.

9 **Body dysmorphic disorder (BDD)**

9.1 Medication is not recommended for the treatment of mild severity BDD. Non pharmacological treatment option only should be used.

9.2 **Medicine choice in the management of body dysmorphic disorder (BDD)**

<table>
<thead>
<tr>
<th>Table 7: NICE: Medicine choice\textsuperscript{10}</th>
<th>Options</th>
<th>Medicine choice</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line</strong></td>
<td>Moderate severity — fluoxetine (off-label).</td>
<td>If severe, consider augmentation with CBT. Anxiolytics may be used cautiously for short periods to counter early activation of SSRIs.</td>
<td></td>
</tr>
<tr>
<td><strong>Second line</strong></td>
<td>Other SSRIs, Clomipramine (off-label).</td>
<td>If poor response to first line treatment at twelve weeks.</td>
<td></td>
</tr>
<tr>
<td><strong>Third line</strong></td>
<td>An SSRI plus buspironone.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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9.3 There is more evidence for the use of fluoxetine than other SSRIs in the management of body dysmorphic disorder.

9.4 If there is no response to fluoxetine, the patient should be referred to secondary care.

9.5 If there has been no response to a full trial of at least one SSRI alone, a full trial of combined treatment with CBT (including ERP) and an SSRI, and a full trial of clomipramine alone, then an SSRI plus buspirone or cognitive therapy by a different multidisciplinary team with expertise in BDD should be considered.

9.6 For patients who respond at twelve weeks, treatment should be continued for a further twelve months. If continued beyond twelve months after remission, the need for continued treatment should be regularly reviewed, agreed with the patient and recorded in the notes.

9.7 When reducing or stopping SSRI treatment, the dose should be tapered gradually over several weeks, according to the patient's need.

9.8 Take account of the starting dose, medicine half-life and particular profile of adverse effects when determining rate of reduction.

9.9 The patient should be encouraged to seek advice if they experience significant discontinuation/withdrawal symptoms.

9.10 Antidepressants (excluding SSRIs or clomipramine), anxiolytics or antipsychotic as monotherapy should not normally be used without appropriate comorbidity. Anxiolytics may be used cautiously for short periods to counter early activation of SSRIs.

10 Social phobia

10.1 Medicine choice in the management of social phobia

See table below

<table>
<thead>
<tr>
<th>Options</th>
<th>Medicine choice</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line</td>
<td>An SSRI e.g. sertraline, citalopram (off-label), escitalopram</td>
<td>Escitalopram should only be used if other SSRIs are not appropriate (contra indicated) or have been tried and ineffective.</td>
</tr>
<tr>
<td>Second line</td>
<td>Paroxetine, or venlafaxine</td>
<td></td>
</tr>
<tr>
<td>Second line</td>
<td>Phenelzine, moclobemide (off-label).</td>
<td></td>
</tr>
</tbody>
</table>

10.2 The patient should be informed of:

- the risk of early activation of symptoms with SSRIs and SNRIs.
- the gradual development, over two weeks or more, of the full anxiolytic effect
• the importance of taking medication as prescribed, reporting side effects, to discuss any concerns about stopping medication with the prescriber, and the need to continue treatment after remission to avoid relapse\(^4\).

10.3 People aged under 30 years who are offered an SSRI or SNRI:

• should be warned them that these medicines are associated with an increased risk of suicidal thinking and self-harm.
• should be seen within one week of first prescribing and the risk of suicidal thinking and self-harm monitored weekly for the first month\(^4\).

10.4 For people who develop side effects soon after starting a medicine, one of the following strategies should be considered:

• monitoring the person's symptoms closely (if the side effects are mild and acceptable to the person).
• reducing the dose of the medicine.
• stopping the medicine and offering either an alternative medicine or individual CBT\(^4\).

10.5 Response is usually seen within eight weeks\(^3\). Twelve weeks should be allowed to assess if any medicine response\(^1,4\).

10.6 Standard antidepressant starting doses are well tolerated\(^3\). Higher doses of SSRIs are not routinely recommended, but individual patients may benefit.

10.7 Medication should be continued for a further six months in patients responding at twelve weeks\(^4\). Treatment should be continued for at least year and probably longer\(^3\).

10.8 When stopping a pharmacological intervention, the dose of the medicine should be reduced:-

• Gradually. If symptoms reappear after the dose is lowered or the medicine is stopped, consider increasing the dose, reintroducing the medicine or offering individual CBT\(^4\).
10.9 If there is no response to an SSRI, a referral should be made to secondary care.

10.10 Benzodiazepines have a rapid effect and can be useful on an ‘as required’ basis.

11 Simple phobia

11.1 Medicine choice in the management of simple phobia

There is no NICE guidance for the management of simple phobia. Medication has a limited role.

12 Long-term use of benzodiazepines

12.1 The use of benzodiazepines should be short-term because of problems with side effects and dependence.

12.2 Repeat benzodiazepine prescriptions should be reserved for the treatment of patients already prescribed long-term treatment with benzodiazepines.

12.3 All patients should be made aware of the risks of dependence if they continue benzodiazepines in regular dosage over a longer period. A clinical judgement has to be made as to whether alternatives may be more suitable, for each patient, and for each proposed medication.

12.4 Many patients are able to take short courses of benzodiazepines (or to use them on an ‘as required’ basis) quite safely and to stop them when no longer needed. If treatment courses lasting longer than four weeks are required, this should not necessarily be regarded as a deviation from good clinical practice, although continuing vigilance of potential hazards is needed throughout treatment.

12.5 If there is no history of drug dependence, and positive indicative ‘lifestyle’ factors are present, a conscious decision to continue benzodiazepine treatment may be more reasonable than the alternatives, provided the patient periodically attempts to slowly reduce the dosage at regular intervals and tries to stop altogether when or if possible.

12.6 If the alternative to benzodiazepine treatment is the use of another form of treatment, either psychological or pharmacological, which proves to have little benefit in practice, a patient may return to the prescriber and ask to be put back on a benzodiazepine. This request should not be automatically declined, but there should be a sympathetic consideration of whether or not this is appropriate.

12.7 There is increasing evidence that long-term prescribing (especially of more than 30 mg diazepam equivalent per day) may cause harm. Clinicians may be faced with requests to continue a prescription for maintenance benzodiazepines. To prevent symptoms of benzodiazepine withdrawal, the clinician should continue the prescription but the dose should be gradually reduced to zero. Very rarely should doses of more than 30 mg diazepam equivalent per day be prescribed.
12.8 Prescribing to assist withdrawal should only be initiated where there is clear evidence of benzodiazepine dependency from the patient’s history, observed symptoms and drug testing. The aim should be to prescribe a reducing regimen for a limited period of time.

12.9 Longer-term prescribing of benzodiazepines should adhere to the general principle of management, including clear indications of benzodiazepine dependence, clear intermediate treatment goals and milestones, regular review and methods to prevent diversion. The clinician should aim for the lowest dose of diazepam that will prevent withdrawal symptoms.

12.10 The rate of withdrawal is often determined by an individual’s capacity to tolerate symptoms. Benzodiazepines, including diazepam, can be withdrawn in proportions of about one-eighth (between one-tenth and one-quarter) of the daily dose every fortnight. In dependence on therapeutic doses, the dose can be reduced initially by 2–2.5 mg and if withdrawal symptoms occur, then the dose can be maintained until symptoms improve. If the patient is not coping and is experiencing severe withdrawal symptoms, it may be necessary to increase the dose to alleviate the symptoms.

12.11 If very high dose prescribing is required, the patient should be referred for specialist assessment. Specialist practitioners then need to exercise caution in their assessments and prescribing. If the patient is stable and free of withdrawal symptoms, at for example 50 mg a day, the dose should be gradually reduced at a faster rate than suggested, for example by half over six weeks and then the planned rate of reduction should be again reviewed in line with the guidance outlined previously. This faster rate of reduction from very high doses led to no convulsions even in a group who had a high incidence of these during previous benzodiazepine withdrawals.

12.12 In the inpatient setting, it is appropriate to provide a slow withdrawal regimen over one to four weeks, with diazepam starting at a daily dose of no more than 30 mg, and usually less, given in divided doses.

12.13 If the patient is in agreement, benzodiazepines should be withdrawn in line with the following considerations:

Switching to diazepam – patients should be offered the equivalent dose of diazepam as it has a long half-life. The approximately equivalent doses are in table 10.

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>Approximate dose (mg) equivalent to 10mg diazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlordiazepoxide</td>
<td>25 - 30mg</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>1-2mg</td>
</tr>
<tr>
<td>Loprazolam*</td>
<td>1mg</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1mg</td>
</tr>
<tr>
<td>Lorazepametazepam*</td>
<td>1mg</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>10mg</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>30mg</td>
</tr>
<tr>
<td>Temazepam</td>
<td>20mg</td>
</tr>
</tbody>
</table>

*These are non-formulary medicines.

Diazepam substitution may not be appropriate for patients with hepatic dysfunction.
12.14 Table 11 shows a suggested taper schedule; some patients may tolerate a more rapid reduction and others may require a slower taper.

<table>
<thead>
<tr>
<th>Table 11: Suggested schedule for reducing dosage of benzodiazepines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduce by 10mg/day every one to two weeks to a daily dose of 50mg</td>
</tr>
<tr>
<td>Reduce by 5mg/day every one to two weeks to a daily dose of 30mg</td>
</tr>
<tr>
<td>Reduce by 2mg/day every one to two weeks to a daily dose of 20mg</td>
</tr>
<tr>
<td>Reduce by 1mg/day every one to two weeks until stopped.</td>
</tr>
</tbody>
</table>

12.15 Usually no more than one week’s supply (exact number of tablets) should be issued at any one time. Gradual dose reduction accompanied by psychological intervention is more likely to be successful than dose reduction alone.

13 Pregnancy

13.1 When choosing a tricyclic antidepressant, selective serotonin reuptake inhibitor or (serotonin-) noradrenaline reuptake inhibitor, take into account:
- the woman’s previous response to these medicines;
- the stage of pregnancy;
- what is known about the reproductive safety (for example, the risk of foetal cardiac abnormalities and persistent pulmonary hypertension in the newborn baby), the risk of discontinuation symptoms in the woman and neonatal adaptation syndrome in the baby with most of the above antidepressants, in particular paroxetine and venlafaxine.
- the views of the woman.

13.2 There is most experience with amitriptyline (constipation and sedation can be a problem with both; withdrawal symptoms may occur), sertraline (low infant exposure) and SSRIs may have increased chance of earlier delivery and reduced birth weight. Paroxetine may be less safe than other SSRIs.

13.3 When assessing the risks and benefits of the above antidepressants for a woman who is considering breastfeeding, take into account:
- the benefits of breastfeeding;
- the uncertainty about the safety of these medicines for the breastfeeding baby;
- the risks associated with switching from or stopping a previously effective medication.

13.3 If a woman who is taking a TCA, SSRI or (S)NRI for an anxiety disorder becomes pregnant, the following options should be discussed with her:

a. stopping the medication gradually and switching to a high-intensity psychological intervention (for example, CBT) continuing with medication if she understands the risks associated with the medication and the mental health problem in pregnancy and the postnatal period and:
  - has expressed a preference for medication or
  - declines psychological interventions; or
  - her symptoms have not responded to psychological interventions
b. changing medication if there is a medicine that is effective for her with a lower risk of adverse effects
  - combining medication with a high-intensity psychological intervention (for example, CBT) if the woman understands the risks associated with the
medication, the mental health problem in pregnancy, the postnatal period and there is no or a limited response, to a high intensity psychological intervention alone.\(^\text{14}\)

13.4 Benzodiazepines should not be offered to women in pregnancy and the postnatal period except for the short-term treatment of severe anxiety and agitation. The gradual withdrawal of benzodiazepines should be considered in women who are planning a pregnancy, pregnant or considering breastfeeding. Benzodiazepines are probably not teratogenic, but are best avoided in late pregnancy. Third trimester use is commonly associated with neonatal difficulties (floppy baby syndrome).\(^\text{3}\)

13.5 When assessing the risks and benefits of antipsychotic medication for a pregnant woman, risk factors for gestational diabetes and excessive weight gain should be taken into account. When choosing an antipsychotic, the limited data on the safety of these medicines in pregnancy and the postnatal period should be taken into account. Prolactin levels in women who are taking prolactin-raising antipsychotic medication and planning a pregnancy should be measured because raised prolactin levels reduce the chances of conception. If prolactin levels are raised, a prolactin-sparing antipsychotic should be considered. If a pregnant woman is stable on an antipsychotic and likely to relapse without medication, she should be advised to continue the antipsychotic. Olanzapine is one of the antipsychotic where there is most experience. Gestational diabetes may be a problem. Adverse metabolic effects should be screened for.\(^\text{3}\)

13.6 There are no adequate data from the use of pregabalin in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Pregabalin should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus). Pregabalin is excreted into human milk. The effect of pregabalin on newborns/infants is unknown. A decision must be made whether to discontinue breast-feeding or to discontinue pregabalin therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.\(^\text{15}\)

13.7 Treatment should not be stopped abruptly and should not routinely be stopped. The woman should also be advised not to stop treatment without medical supervision.
14 Older adults

Table 12: A guide to medication doses of commonly used psychotropics in older adults

<table>
<thead>
<tr>
<th>Medicines</th>
<th>Specific indication/ additional notes</th>
<th>Starting dose</th>
<th>Usual maintenance dose</th>
<th>Maximum dose in the elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Anxiety disorder</td>
<td>10mg in the morning</td>
<td>10-20mg in the morning</td>
<td>20mg in the morning</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>Phobic and obsessional states</td>
<td>10mg at night (dose increases should be cautious)</td>
<td>10-20mg in the morning</td>
<td>20mg in the morning</td>
</tr>
<tr>
<td>Fluoxetine (caution as long half-life and inhibitor of several CYP enzymes)</td>
<td>Anxiety disorder</td>
<td>20mg in the morning</td>
<td>20mg in the morning</td>
<td>40mg in the morning</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Anxiety disorder</td>
<td>25-50mg in the morning (25mg can be increased to 50mg in the morning after one week)</td>
<td>50-100mg in the morning</td>
<td>100mg (occasionally up to 150mg in the morning)</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Anxiety disorder. Monitor BP on initiation</td>
<td>37.5mg in the morning (increased to 75mg in the morning after one week)</td>
<td>75-150mg in the morning</td>
<td>150mg in the morning (occasionally 225mg daily is necessary)</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Generalised anxiety disorder. Dose adjustment based on renal function (see product information)</td>
<td>25mg twice a day (increase by 25mg twice a day weekly). Up to 75mg twice a day (if healthy and normal renal function)</td>
<td>Usually 150mg/day. Up to 150mg twice a day (if healthy and normal renal function)</td>
<td>150-300mg/day</td>
</tr>
</tbody>
</table>

Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

15 Medicine –induced hyponatraemia

Antidepressant-induced hyponatraemia

15.1 Hyponatraemia with antidepressants should be considered, especially serotonergic medicines. The onset is usually within thirty days of starting treatment. Symptoms include headache, dizziness, nausea, vomiting, confusion, malaise, restlessness, lethargy, cramps, disorientation and seizures. Risk factors include history of hyponatraemia, low body weight, older or female patients, low baseline sodium concentration, reduced renal function, warm weather, medical comorbidity and some medicines.

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

15.3 Medicines which may be a risk factor for developing hyponatraemia include carbamazepine, antipsychotics, diuretics, non-steroidal medicines, cancer chemotherapy, calcium antagonists and angiotensin converting enzyme inhibitors.

15.4 The normal range for serum sodium is 135 – 145mmol/l (Whittington ICE).
15.5 If the serum sodium is >125mmol/l, monitor sodium until normal. If the serum
sodium is < 125mmol/l, a referral to specialist medical care should be made as there is an increased risk of seizures, coma and respiratory arrest. The antidepressant should be discontinued immediately.

15.6 The withdrawal of other medicines associated hyponatraemia should be considered if possible.

15.7 An antidepressant of a different class should be considered; for example, mirtazapine or moclobemide. A low dose should be commenced, increasing slowly and monitoring closely. If hyponatraemia recurs and continued antidepressant use is essential, water restriction and/or careful use of demeclocycline should be considered with specialist input.

Antipsychotic-induced hyponatraemia

15.7 Case reports and case series implicate antipsychotics including olanzapine. Syndrome of inappropriate antidiuretic hormone usually develops in the first weeks of treatment. Monitoring of plasma sodium is desirable for all those receiving antipsychotics. Signs of confusion or lethargy should provoke diagnostic analysis including plasma sodium and urine osmolality.

15.8 See the Choice and Medication link for leaflet on hyponatraemia.

16 Weight gain

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

16.2 Olanzapine is considered to have a high risk of causing weight gain. Refer to the Maudsley prescribing guidelines for other antipsychotics.

16.3 It is common for pregabalin to cause weight gain. In accordance with current clinical practice, some diabetic patients who gain weight on pregabalin treatment may need to adjust hypoglycaemic medicines.

16.4 A weight gain advice leaflet and a leaflet on metabolic syndrome are available on the Choice and Medication link on the intranet.

17 Co-morbid diabetes

17.1 Serotonin reuptake inhibitors have a favourable effect on diabetic parameters in patients with type II diabetes. Insulin requirements may be decreased. Fluoxetine has been associated with improvements in HbA1c levels and reduced insulin requirements. Sertraline may also reduce HbA1c. Long-term use of serotonin reuptake inhibitors may increase the risk of diabetes to a modest extent, but also evidence of no effect. Serotonin-noradrenaline reuptake inhibitors do not appear to disrupt glycaemia control. Little is known of the effect of mirtazapine in diabetes. Tricyclic antidepressants are associated
with increased appetite and hyperglycaemia. Clomipramine has been reported to precipitate diabetes. Long-term use of diabetes seems to increase risk of diabetes. Irreversible mono-amine oxidase inhibitors have a tendency to cause extreme hypoglycaemia episodes\(^3\).

17.2 Olanzapine is strongly linked to impaired glucose tolerance, diabetes and diabetic ketoacidosis. Refer to the Maudsley prescribing guidelines for other antipsychotics\(^3\).

17.3 Pregabalin has been shown to have efficacy in trials in diabetic neuropathy\(^15\).

17.4 A leaflet on metabolic syndrome is available on the Choice and Medication link on the intranet.

18 Dyslipidaemia

18.1 Olanzapine appears to have the greatest propensity to increase lipids compared to other antipsychotics\(^3\).

19 Medicine interactions

19.1 SSRIs should not normally be offered to patients taking non-steroidal anti-inflammatory medicines because of the increased risk of gastrointestinal bleeding. An antidepressant with a lower propensity to cause this should be offered e.g. mirtazapine depending on the indication. If a suitable alternative cannot be identified, a gastroprotective medicines should be prescribed concurrently with the SSRI\(^19\).

19.2 SSRIs should not normally be offered to patients prescribed warfarin, aspirin or heparin because of their anti-platelet effect. Mirtazapine can be offered depending on the indication. The international normalised ratio (INR) may be increased slightly\(^19\).

19.3 If aspirin is used as a single agent, mirtazapine can also be offered depending on the indication. If a suitable alternative cannot be identified, a gastroprotective medicine should be prescribed concurrently with the SSRI\(^19\).

19.4 SSRIs should not normally be offered to patients prescribed a triptan medicine for migraine. Mirtazapine can be offered depending on the indication\(^19\).

19.5 Fluoxetine or paroxetine should not be offered to patients prescribed atomoxetine. A different SSRI can be offered\(^19\).

19.6 SSRIs should not be offered at the same time as a monoamine oxidase B inhibitor e.g. selegiline. Mirtazapine can be offered depending on the indication\(^19\).

19.7 Sertraline is a preferred antidepressant for patients prescribed flecainide or propafenone, although mirtazapine can be used depending on the indication\(^19\).

19.8 Pregabalin may potentiate the effects of ethanol and lorazepam. In the postmarketing experience, there are reports of respiratory failure and coma in patients taking pregabalin and other central nervous system (CNS) depressant
medicinal products. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone\textsuperscript{15}.

19.9 The metabolism of olanzapine may be induced by smoking and carbamazepine, which may lead to reduced olanzapine concentrations. The clinical consequences are likely to be limited, but clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary\textsuperscript{20}.

19.9 Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. A lower starting dose of olanzapine should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin. A decrease in the dose of olanzapine should be considered if treatment with an inhibitor of CYP1A2 is initiated\textsuperscript{20}.

19.11 Olanzapine may antagonise the effects of direct and indirect dopamine agonists\textsuperscript{20}.

19.12 The concomitant use of olanzapine with anti-Parkinsonian medicinal products in patients with Parkinson’s disease and dementia is not recommended\textsuperscript{20}.

20 Dissemination and implementation arrangements

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

21 Training requirements

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

22 Monitoring and audit arrangements

See table below.
<table>
<thead>
<tr>
<th>Element to be monitored</th>
<th>Lead</th>
<th>How Trust will monitor compliance</th>
<th>Frequency</th>
<th>Reporting arrangements</th>
<th>Acting on recommendation(s) and Lead(s)</th>
<th>Change in practice and lessons to be shared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulary adherence</td>
<td>Chief Pharmacist</td>
<td>ePACT data Clinical pharmacy checks</td>
<td>ongoing</td>
<td>Drugs and Therapeutics Group</td>
<td>Drugs and Therapeutics Group</td>
<td>Review of policy; implementation practices and procedures. Re- audit Give feedback to prescribers.</td>
</tr>
</tbody>
</table>

23 Review of the policy

These guidelines shall be reviewed in 3 years or earlier should a new guideline or change of practice came to light.
References


18. Pfizer Ltd. The specification of product characteristics: Lustral 100mg tablets. November 2015 (online)


