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SECTION 1: THE TREATMENT OF DEPRESSION

Formulary and Prescribing Guidelines

1.1 Introduction

This guidance should be considered as part of a stepped care approach in the management of depressive disorders. Antidepressants are not routinely recommended for persistent sub-threshold depressive symptoms or mild depression but can be considered in these categories where there is a past history of moderate or severe depression, initial presentation of sub-threshold depressive symptoms for at least 2 years, and persistence of either mild or sub-threshold depression after other interventions[1] have failed. The most current NICE guidance should be consulted wherever possible to obtain the most up to date information.

For individuals with moderate or severe depression, a combination of antidepressant medication and a high intensity psychological intervention (CBT or IPT) is recommended.

When depression is accompanied by symptoms of anxiety, usually treat the depression first. If the person has an anxiety disorder and co-morbid depression or depressive symptoms, consider treating the anxiety first. Also consider offering advice on sleep hygiene, by way of establishing regular sleep and wake times; avoiding excess eating, avoiding smoking and drinking alcohol before sleep; and taking regular physical exercise if possible.

Consider tests for thyroid dysfunction for patients with depression or unexplained anxiety.[7]

If used in pregnancy, refer to the MHRA warning [9] for SSRI and SNRIs, about the small increased risk of postpartum haemorrhage when used in the month before delivery. See formulary section 20 (Antenatal and postnatal prescribing).

Detailed information on the treatment of depression in children and adolescents can be found in section 12. Further guidance on prescribing for older adults and for antenatal/postnatal service users can be found in section 11 and section 20, respectively.

Antidepressants, although not considered to be dependence forming medicines, can cause withdrawal symptoms when they are stopped. This possibility should be explained to patients so that a shared decision can be reached about the benefits and risks of treatment, including that missed doses or sudden cessation may lead to symptoms of withdrawal and that support will be provided at the time that reduction or discontinuation is appropriate.

Factors which may increase the risk of problems during withdrawal, such as long duration of use, high dose, history of withdrawal symptoms and taking an antidepressant with a short half-life should be considered. See section 1.3 of this document for more information.

This document refers to the use of medicines to treat depression in patients who are considering medicines as a treatment for depression. Other treatments for depression such as psychological treatments and digitally enabled therapies, vagus nerve stimulation, repetitive transcranial magnetic stimulation (rTMS) and electroconvulsive therapy (ECT), are available and play important roles in the treatment of depression. This guidance does not make specific reference to their use or place in therapy nor does it aim to promote the use of medicines over other treatments. For guidance on their use and place in therapy refer to:

- EPUT Electroconvulsive therapy (ECT) Policy and procedural guidelines – CLP 26 & CLPG26

- EPUT Repetitive Transcranial Magnetic Stimulation (rTMS) Policy and procedural guidelines – CLP82 & CLPG82
- EPUT Vagus Nerve Stimulation (VNS) Policy CLP85
- NICE Guideline – NG222 Depression in adults: treatment and management
- NICE Health Technology Evaluation (HTE) – HTE 8 Digitally enabled therapies for adults with depression: early value assessment
- NICE, Interventional Procedures Guidance (IPG) – IPG542 Repetitive transcranial magnetic stimulation for depression
- NICE, Interventional Procedures Guidance (IPG) – IPG679 Implanted vagus nerve stimulation for treatment-resistant depression

1.2 Approved Medicines for the treatment of Depression in Adults

For licensing indications, see Annex 1

Medicine[5]	Formulation[5]	Comments[2,3,4]
Amitriptyline	Tabs 10mg, 25mg, 50mg Liquid 50mg/5ml	TCA Tricyclic Antidepressant
Citalopram	Tabs 10mg, 20mg, 40mg Drops 40mg/ml (1drop=2mg) 4 drops (8 mg) ≡ 10mg tablet	SSRI Selective Serotonin Reuptake Inhibitor Bioequivalence varies between tablets and liquid
Clomipramine	Caps 10mg, 25mg, 50mg	TCA
Dosulepin	Caps 25mg Tabs 75mg	TCA For existing patients only, if no contra-indication.
Duloxetine	Caps 30mg, 60mg	4th line for depression. 3rd line for adults over 65.
Escitalopram	Tabs, 5 mg; 10 mg Oral drops, 10 mg/mL; 20 mg/mL	SSRI Selective Serotonin Reuptake Inhibitor
Fluoxetine	Caps 20mg, Liquid 20mg/5ml	SSRI
Flupentixol	Tabs 500mcg, 1mg	'Other' antidepressant
Imipramine	Tabs 10mg, 25mg Liquid 25mg/5ml	TCA
Lofepramine	Tabs 70mg Liquid 70mg/5ml	TCA

Medicine[5]	Formulation[5]	Comments[2,3,4]
Mirtazapine	Tabs 15mg, 30mg, 45mg Orodispersible Tabs 15mg, 30mg, 45mg Liquid 15mg/ml	NaSSa Noradrenaline and Specific Serotonin antidepressant
Moclobemide	Tabs 150mg, 300mg	RIMA Reversible Inhibitor of Monoamine A
Paroxetine	Tabs 20mg, 30mg	SSRI
Phenelzine	Tabs 15mg	MAOI
Sertraline	Tabs 25mg, 50mg, 100mg	SSRI
Trazodone	Caps 50mg, 100mg Tabs 150mg Liquid 50mg/5ml	Tricyclic-related antidepressant
Venlafaxine	Tabs 37.5mg, 75mg M/R Caps 75mg, 150mg	Doses above 300mg monitoring required. Cardiac risk. Consultant supervision.
Vortioxetine	Tabs 5mg, 10mg, 20mg	Serotonin Modulator and Stimulator 3rd line – see note below**
Lithium	See F&PG section 3 – treatment of bipolar affective disorder for details on approved preparations	
Antipsychotics	See F&PG section 3 – treatment of psychosis for details on approved preparations Check individual medicines for licensed uses	
Lamotrigine	See F&PG section 3 – treatment of bipolar affective disorder for details on approved preparations - Off-label use in depression	
Triiodothyronine / Liothyronine	Caps 5 micrograms, 10 micrograms, 20 micrograms	For use within EPUT not to be transferred to primary care., Consultant initiation only

Agomelatine is non formulary based on the guidance provided by NICE in relation to the termination of TA 231, July 2011 (due to the lack of evidence to support use).

Esketamine Nasal Spray is non formulary based on the guidance provided by NICE in relation to the recommendations of TA 854, December 2023 and the terminated TA899, June 2023.

Trimipramine is non formulary as it does not represent a cost-effective choice of TCA.

Vortioxetine is the subject of a NICE Technology Appraisal (TA 367) and is approved for treatment of major depressive episodes in adults which have been unresponsive to two previous antidepressants.

1.3 NICE Clinical Guidelines

NICE NG222 Depression in adults: treatment and management (June 2022)[4]
NICE CG91: Depression in adults with a chronic physical health problem: recognition and management (October 2009) [8]
NICE NG134: Depression in children and young people identification and management[11]

1.3.1 Choice of antidepressant

- Make a shared decision with the person about their treatment. See the NICE guideline on shared decision making[10]

- Use the NICE visual summaries from NG222 – Depression in adults: discussing first-line treatments for less severe depression and Depression in adults: discussing first-line treatments for more severe depression to support decision making

    - https://www.nice.org.uk/guidance/ng222/resources/discussing-firstline-treatments-for-less-severe-depression-pdf-11131007006

    - https://www.nice.org.uk/guidance/ng222/resources/discussing-firstline-treatments-for-more-severe-depression-pdf-11131007007

- Consider using a baseline assessment for severity of depression and regularly review symptoms both clinically and using standard severity rating scales. Initially, normally **choose a generic SSRI** whilst taking the following into account:

    - Fluoxetine, fluvoxamine and paroxetine have a higher propensity for pharmacological interactions (*see current BNF*). It may be appropriate to consider sertraline and citalopram in patients who have chronic health problems, as these have a lower propensity for interactions with medications for physical health problems *(see table below)*

    - Paroxetine has a higher incidence of discontinuation symptoms (consider half-lives) and greater effect on muscarinic receptors. *See section 1.3*

    - Medicines that affect the serotonin transporters such as SSRIs and SNRIs are associated with an increased risk of bleeding – use only where alternatives are not appropriate after assessing the risks and benefits and consider prescribing a gastro-protective medication (e.g. omeprazole) in older adults who are taking NSAIDs and/or aspirin although be aware this only

    - The risk of suicide attempted suicide or self-harm. Mirtazapine, venlafaxine and trazadone have been associated with the highest absolute risk.

- The risk of "switching" or the precipitation of mania/hypomania particularly in patients who may have undiagnosed bipolar disorder
- Acquisition cost

- Discuss choice of antidepressant, covering:
  - Patient choice - the patient's perception of the efficacy and tolerability[4]
  - Existing co-morbid psychiatric disorders such as obsessive compulsive disorder, anxiety spectrum disorder etc., through accurate history taking (Annex 1)
  - Anticipated adverse events – for example, agitation, nausea and vomiting (with SSRI antidepressants), and discontinuation symptoms (*see* Annex 2).

- Consider using tools to support patients to be involved in decision making such as handy charts and information leaflets on the Choice and medication Website www.choiceandmedication.org/Eput

- Ensure that patient understand that side effects may be experienced before any beneficial effect and that many will ease with time)

- Potential interactions with concomitant medication or physical illness (there is currently no evidence to support using specific antidepressants in particular physical health problems)

Medication for physical health problem	**Recommended antidepressant(s)[4]**
NSAIDs (non-steroidal anti-inflammatory drugs)	Do not normally offer SSRIs – but if no suitable alternatives can be identified, offer gastro-protective medicines (for example, proton pump inhibitors) together with the SSRI. Consider mirtazapine, moclobemide or trazodone
Warfarin or heparin	Do not normally offer SSRIs. Consider mirtazapine.
Theophylline, clozapine, or methadone	Do not normally offer fluvoxamine – offer sertraline or citalopram
'Triptan' medication for migraine	Do not offer SSRIs – offer mirtazapine or trazodone.
Aspirin	Use SSRIs with caution – if no suitable alternatives can be identified, offer gastro-protective medicines together with the SSRI. Consider trazodone when aspirin is used as a single agent. Alternatively, consider mirtazapine.
Monamine oxidase B inhibitors (for example, selegiline or rasagiline)	Do not normally offer SSRIs – offer mirtazapine or trazodone.
Flecainide or propafenone	Offer sertraline as the preferred antidepressant – mirtazapine or moclobemide may also be used.

- When prescribing antidepressants for older adults *(see section 11 for further information)*

    - Prescribe at an age-appropriate dose taking into account person's general physical health, comorbidities and possible interactions with any other medicines they may be taking (see table above)

    - Monitor carefully for side-effects (*see* Annex 2) Consider using structured side effect rating scale such as the antidepressant side effect checklist (ASEC)

    - be alert to an increased risk of falls and fractures

    - be alert to the risks of hyponatraemia (particularly in those with other risk factors for hyponatraemia, such as concomitant use of diuretics).

- When prescribing medicines other than SSRIs, take into account:

    - The increased likelihood of the person stopping treatment because of side effects, and the consequent need to increase the dose gradually, as for example with venlafaxine and tricyclic antidepressants (TCAs)

    - That dosulepin should not be prescribed

    - That irreversible Monoamine oxidase inhibitors MAOIs (such as phenelzine) should only normally be prescribed by a Consultant Psychiatrist.

- General Issues

    - Explore any concerns that the person may have about taking an antidepressant and provide information about:

    - The gradual development of the full antidepressant effect

    - The importance of taking the medication as prescribed and the need to continue beyond remission

    - Potential side effects and pharmacological interactions and strategies for minimisation

    - The risk and nature of discontinuation symptoms (particularly with medicines with a shorter half-life, such as paroxetine and venlafaxine)

    - The fact that addiction does not occur

    - The risk of clinical worsening, suicidal thoughts and ideation. (see 1.2.2)

- Do not prescribe or advise use of St John's Wort for depression

    - Explain the different potencies of the preparations available and the potential serious interactions of St John's Wort with other medicines (including oral contraceptives, anticoagulants and anticonvulsants)

- Patients receiving ECT can be prescribed antidepressants simultaneously and there is evidence that there is a synergistic effect when antidepressants are used.

In every instance, choice of antidepressant should be based on the circumstances of the individual being treated and their individual preferences. If after consultation a range of choices are available taking into consideration safety and concordance profiles, the medicine of lowest acquisition cost should be selected.

1.3.2 Risk of clinical worsening, suicidal Ideation, suicidal attempts and suicide

The period when someone starts an antidepressant has been associated with an increase in suicidal thoughts. This may be due to a number of factors and not just the initiation of the antidepressant itself however, antidepressants all carry a warning about the increased risk of suicide, suicidal thought, suicidal attempts and clinical worsening.

- Take into account toxicity in overdose for people at significant risk of suicide. When initiating antidepressants, especially SSRIs, actively monitor suicidal ideations, self-harming thoughts and changes in both. If changes are noticed, increase review frequency. Be aware that:
    - Compared with other equally effective antidepressants recommended in primary care (such as SSRIs), venlafaxine is associated with a greater risk of death from overdose, but the greatest risk in overdose is with TCAs, except for lofepramine
    - For people who are not considered to be at increased risk of suicide, normally review after 2 weeks, then regularly every 2–4 weeks in the first 3 months for example, and then at longer intervals if response is good
    - For people who are considered to be at **increased risk of suicide** or are younger than25 years assess their mental state and mood before starting the prescription, ideally in person (or by video call or by telephone call if in-person assessment is not possible, or not preferred)
    - In the early stages of treatment, the motivation tends to improve first whilst mood improvement may take longer, therefore there is a risk that the motivation for suicide may increase and this should be closely monitored. Be aware of the possible increased prevalence of suicidal thoughts, self-harm and suicide in the early stages of antidepressant treatment particularly before notable changes in mood have occurred, and ensure that a risk management strategy is in place. Psycho-education and engaging carers is important to reduce the risk of suicide or attempted suicide.
    - Review them 1 week after starting the antidepressant medication or increasing the dose for suicidality (ideally in person, or by video call, or by telephone if these options are not possible or not preferred)
    - Review them again after this as often as needed, but no later than 4 weeks after the appointment at which the antidepressant was started

- Base the frequency and method of ongoing review on their circumstances (for example, the availability of support, unstable housing, new life events such as bereavement, break-up of a relationship, loss of employment), and any changes in suicidal ideation or assessed risk of suicide

- consider routine outcome monitoring (using appropriate validated sessional outcome measures, for example PHQ-9) and follow up

1.3.3 Early treatment with an antidepressant[4]

If increased anxiety or agitation develops early in treatment with an SSRI, a short period of concomitant therapy (usually no longer than 2 weeks) with a benzodiazepine may be considered[4]. (This consideration does not apply to patients with chronic anxiety and benzodiazepines should only be used with caution in patients at risk of falls[4].) The patient should be informed that this is usually a transient effect and should last no longer than a few weeks. If the anxiety or agitation is unacceptable to the patient, consider changing to a different antidepressant (*see below*).

1.3.4 Lack of response to initial antidepressant[4]

- Use the NICE visual summary from NG222 – Depression in adults: further-line treatment to support decision making

  - https://www.nice.org.uk/guidance/ng222/resources/furtherline-treatment-pdf-11131007009

- If improvement is not reported within 2-4 weeks, check that the medication has been taken as prescribed and enquire about side-effects experienced (*see* Annex 2 *for side effect profile).* Discuss further treatment options with the person and make a shared decision on how to proceed based on their clinical need and preferences considering both pharmacological and non-pharmacological options. If the patient prefers medication consider:

- If response is absent or minimal after 3–4 weeks of treatment with a therapeutic dose of an antidepressant, increase support and consider increasing the dose in line with the summary of product characteristics (SPC) if there are no significant side effects. If there are side effects or if the patient prefers, consider switching to another antidepressant.

- For guidance on switching antidepressants see

  - https://www.sps.nhs.uk/articles/planning-and-agreeing-an-antidepressant-switching-strategy/

- If there is some improvement by week 4, continue treatment for another 2-4 weeks. Consider increasing the dose in line with the summary of product characteristics (SPC) if there are no significant side effects Consider switching to another antidepressant if response is still not adequate; there are side effects; or if the patient prefers to change medication

- Be aware that **higher doses** of antidepressants **may not be more effective** and can increase the frequency and severity of side effects; ensure follow-up and frequent monitoring of symptoms and side effects after dose increases

- If considering switching antidepressant, **consider a different SSRI** or **an antidepressant from a different class.**

- If switching medication consider that a period of cross-tapering may be needed. The Maudsley Guidelines, Psychotropic Drug Directory and Specialist Pharmacy Service provide guidance on switching medications

- If a person's depression has not responded to either pharmacological or psychological interventions, consider combining antidepressants with CBT.

- If a person whose depression has had no response or a limited response to antidepressant medication does not want to try a psychological therapy, and instead wants to try a combination of medications, explain the possible increase in their side-effect burden.

- If a person with depression wants to try a combination treatment and is willing to accept the possibility of an increased side-effect burden consider:

    - adding an additional antidepressant medication from a different class (for example, adding mirtazapine or trazodone to an SSRI)

    - combining an antidepressant medication with a second-generation antipsychotic (for example, aripiprazole, olanzapine, quetiapine or risperidone) or lithium

    - augmenting antidepressants with electroconvulsive therapy, lamotrigine, or triiodothyronine (liothyronine – currently non-formulary).

- Should augmentation be considered necessary, then advice from a Consultant Psychiatrist should be sought; especially if the patient is based in primary care.

- Be aware that some combinations of classes of antidepressants are potentially dangerous and should be avoided (for example, a SSRI, SNRI or TCA with a MAOI), and that when using an antipsychotic the effects of this on depression, including loss of interest and motivation, should be carefully reviewed.

- The use of some antipsychotics, lamotrigine and triiodothyronine (liothyronine) is off label but is approved for use within EPUT

1.3.5 Guidance for Prescribing Venlafaxine:

- Do not prescribe venlafaxine for patients with:

    - Uncontrolled hypertension

    - Recent myocardial infarction

    - High risk of cardiac arrhythmia

- Monitor BP at initiation and regularly during treatment (particularly during dose titration)

- Monitor for signs and symptoms of cardiac dysfunction

- Doses of 300 mg daily or more should only be prescribed under the supervision or advice of a specialist mental health practitioner

1.3.6 Guidance for prescribing Tricyclic Antidepressants:

Tricyclic antidepressants are cardiotoxic (defined as causing a 25% increase in baseline QTc interval) – even at therapeutic doses. Therefore, it is advisable to perform an ECG and to monitor BP prior to initiating treatment. NICE does specify that people who start on low dose TCAs, and have a clear clinical response can be maintained on that dose with careful monitoring. Dosulepin is the most cardiotoxic, and NICE specifies 'Do not switch or start, dosulepin'.

- Do not routinely augment an antidepressant with:
    - A benzodiazepine for more than 2 weeks
    - Buspirone, carbamazepine, lamotrigine, valproate or thyroid hormones.

1.3.7 Guidance for prescribing Vortioxetine:

Vortioxetine is recommended as an option for treating major depressive episodes in adults whose condition has responded inadequately to two antidepressants within the current episode[6].

- The starting and recommended dose of Vortioxetine is 10 mg once daily in adults less than 65 years of age.

- Depending on individual patient response, the dose may be increased to a maximum of 20 mg vortioxetine once daily, or decreased to a minimum of 5 mg vortioxetine once daily.

1.3.8 Pharmacological management of depression with psychotic symptoms[4]

- Use the NICE visual summary from NG222 – Depression in adults: treatment options for chronic depression, depression with personality disorder or psychotic depression to support decision making
    - https://www.nice.org.uk/guidance/ng222/resources/treatment-options-for-chronic-depression-depression-with-personality-disorder-or-psychotic-depression-pdf-11131007010

- For individuals with depression who have psychotic symptoms consider augmenting their treatment plan with an antipsychotic medication. *(see sections 2 and 3 for further information relating to monitoring required for these medicines)*

- Discuss treatment options and, for those people who have capacity, reach a shared decision based on their clinical needs and preferences. See the visual summary on treatment of psychotic depression.

- If a person with depression with psychotic symptoms does not wish to take antipsychotic medication in addition to an antidepressant, then treat with an antidepressant alone.

- Monitor people with depression with psychotic symptoms for treatment response (in particular for unusual thought content and hallucinations).

- Consider continuing antipsychotic medication for people with depression with psychotic symptoms for a number of months after remission, if tolerated. The decision about if and when to stop antipsychotic medication should be made by, or in consultation with, specialist services.

1.3.9 Pharmacological treatment of depression in a patient with a diagnosis of personality disorder

- Use the NICE visual summary from NG222 – Depression in adults: treatment options for chronic depression, depression with personality disorder or psychotic depression to support decision making

    - https://www.nice.org.uk/guidance/ng222/resources/treatment-options-for-chronic-depression-depression-with-personality-disorder-or-psychotic-depression-pdf-11131007010

- Do not withhold treatment for depression because of a coexisting personality disorder.
- For people with depression and a diagnosis of personality disorder consider a combination of antidepressant medication and a psychological treatment (for example, BA, CBT, IPT or STPP).
- When delivering antidepressant medication in combination with psychological treatment for people with depression and a diagnosis of personality disorder:
    - give the person support and encourage them to carry on with the treatment
    - provide the treatment in a structured, multidisciplinary setting
    - use a validated measure of prospective mood monitoring or a symptom checklist or chart to assess response, or any exacerbation of emotional instability
    - extend the duration of treatment if needed, up to a year.
- For people with depression and a diagnosis of personality disorder, consider referral to a specialist personality disorder treatment programme.
- See the NICE guideline on borderline personality disorder for recommendations on treatment for borderline personality disorder with coexisting depression (CG78).
    - https://www.nice.org.uk/guidance/CG78

1.3.10 Guidance on prescribing antipsychotics

- When prescribing an antipsychotic, monitor weight, fasting lipid and glucose levels, and other relevant side effects (*see F&PG section 2 for full monitoring requirements of antipsychotics)*

- For people with depression who are taking an antipsychotic, consider at each review whether to continue the antipsychotic based on their current physical and mental health risks.

- Only stop antipsychotics in specialist mental health services, or with their advice. When stopping antipsychotics, reduce doses gradually over at least 4 weeks and in proportion to the length of treatment

1.3.11 Guidance on prescribing lithium

- When prescribing Lithium (*for augmentation of the primary antidepressant*) – monitor:

    - Weight, renal and thyroid function and calcium levels before treatment and every 6 months during treatment (more often if there is evidence of renal impairment)

    - For women of reproductive age, in particular if they are planning a pregnancy, discuss the risks and benefits of lithium, preconception planning and the need for additional monitoring.

    - Consider ECG monitoring in people at high risk of cardiovascular disease

    - Monitor serum Lithium levels 1 week after treatment starts and after every dose change until stable, and then every 3 months *(see F&PG section 3 for full details)*

    - Only stop lithium in specialist mental health services, or with their advice. When stopping lithium, whenever possible reduce doses gradually over 1 to 3 months.

1.3.12 Guidance on prescribing tri-iodothyronine (liothyronine)

- Liothyronine can be used in line with NICE guidance, off label, to treat depression not responding to other strategies. Doses are based on maintaining the patient's thyroid hormone levels within normal limits and usual doses of liothyronine are 10 to 50 micrograms daily.

- It is only to be initiated by consultant psychiatrists and prescribing is to remain within EPUT.

- Liothyronine should only be used in patients with normal thyroid function tests at baseline. Patients with tests indicating hypo- or hyper-thyroidism should be referred to the GP for diagnosis and ongoing management.

- When prescribing liothyronine (*for augmentation of the primary antidepressant*) – monitor:

    - Thyroid function tests (TFTs) at baseline

    - Recheck TFTs at 3 months, 6 months and yearly thereafter and additionally after each dose change.

- Continue liothyronine if the TSH level is in the lower normal range or just below and T3/T4 is within the normal range

Monitor bone density every 2 years in postmenopausal women

1.3.13 Maintenance treatment with antidepressents[4]

- Discuss with people that continuation of treatment (antidepressants or psychological therapies) after full or partial remission may reduce their risk of relapse and may help them stay well. Reach a shared decision on whether or not to continue a treatment for depression based on their clinical needs and preferences

- Use the NICE visual summary from NG222 – Depression in adults: preventing relapse to support decision making

  - https://www.nice.org.uk/guidance/ng222/resources/preventing-relapse-pdf-11131007008

- The risk of relapse may be increased in people with the following

  - a history of recurrent episodes of depression, particularly if these have occurred frequently or within the last 2 years

  - a history of incomplete response to previous treatment, including residual symptoms

  - unhelpful coping styles (for example, avoidance and rumination)

  - a history of severe depression (including people with severe functional impairment)

  - other chronic physical health or mental health problems

  - personal, social and environmental factors that contributed to their depression and that are still present (for example, relationship problems, ongoing stress, poverty, isolation, unemployment)

- Discuss the risks of remaining on medication including the increased risk of adverse effects and the increased risk of difficulty stopping the medication.

- Where a patient has responded to a medication and is considered at higher risk of relapse the medication should be continued unless there is a good reason to reduce or replace it. Psychological therapies can be considered alongside medication or as an alternative if the patient does not want to remain on medication.

- Refer to section 1.3 for information on stopping or reducing medicines if the patient wants to reduce or stop their medication.

1.4 Stopping or reducing antidepressants [4, 10]

1.4.1 Warn the patient about withdrawal/ discontinuation symptoms

Advise people taking antidepressant medication that, before stopping it, they should discuss this with their practitioner and should not stop taking their medicines suddenly.

Advise people that if they stop taking antidepressant medication abruptly, miss doses or do not take a full dose, they may have discontinuation symptoms such as:

- Restlessness or agitation
- problems sleeping
- unsteadiness
- sweating
- abdominal symptoms (such as nausea)
- altered sensations (for example electric shock sensations in the head)
- altered feelings (for example irritability, anxiety or confusion).
- palpitations, tiredness, headaches, and aches in joints and muscles.

Explain that whilst the withdrawal symptoms which arise when stopping or reducing antidepressants can be mild and self-limiting, there is substantial variation in people's experience, with symptoms lasting much longer (sometimes months or more) and being more severe for some patients. Symptoms may mimic many of those seen in depression itself however relapse is not likely to occur as quickly after stopping.

Recognise that people may have fears and concerns about stopping their antidepressant medication (for example, the withdrawal effects they may experience, or that their depression will return) and may need support to withdraw successfully, particularly if previous attempts have led to withdrawal symptoms or have not been successful. This could include:

- details of online or written resources that may be helpful
- increased support from a clinician or therapist (for example, regular check-in phone calls, seeing them more frequently, providing advice about sleep hygiene)

When stopping a person's antidepressant medication:

- take into account the pharmacokinetic profile (for example, the half-life of the medication as antidepressants with a short half-life will need to be tapered more slowly) and the duration of treatment
- slowly reduce the dose to zero in a step-wise fashion, at each step prescribing a proportion of the previous dose (for example, 50% of previous dose)
- consider using smaller reductions (for example, 25%) as the dose becomes lower

- if, once very small doses have been reached, slow tapering cannot be achieved using tablets or capsules, consider using liquid preparations if available

- ensure the speed and duration of withdrawal is led by and agreed with the person taking the prescribed medication, ensuring that any withdrawal symptoms have resolved or are tolerable before making the next dose reduction

- take into account the broader clinical context such as the potential benefit of more rapid withdrawal if there are serious or intolerable side effects (for example, hyponatraemia or upper gastrointestinal tract bleeding)

- take into account that more rapid withdrawal may be appropriate when switching antidepressants

- recognise that withdrawal may take weeks or months to complete successfully.

Monitor and review people taking antidepressant medication while their dose is being reduced, both for withdrawal symptoms and the return of symptoms of depression. Base the frequency of monitoring on the person's clinical and support needs. Inform the person that they should seek advice from their practitioner if they experience significant discontinuation symptoms.

Withdrawal symptoms usually occur within 5 days of stopping treatment, or occasionally during taper or after missed doses (short half-life medicines). The perception of symptom severity may be worse if the patient is not warned of the possibility in advance. Some symptoms are more likely with particular medicines.

Patients prescribed short half-life medicines (e.g. paroxetine); patients who have taken an antidepressant for more than 8 weeks; patients who developed anxiety at the start of antidepressant therapy (particularly SSRI's); patients taking other centrally acting medicines (e.g. antihypertensives, antihistamines, antipsychotics); children and adolescents; patients who have experienced discontinuation symptoms before[1] are most at risk of developing discontinuation symptoms.

For further advice on stopping antidepressants see

- NICE guideline [NG215]. Medicines associated with dependence or withdrawal symptoms: safe prescribing and withdrawal management for adults[10]

- Royal College of Psychiatrists Guidance on Stopping antidepressants https://www.rcpsych.ac.uk/mental-health/treatments-and-wellbeing/stopping-antidepressants

- Choice and medication leaflet – stopping or coming off antidepressants https://www.choiceandmedication.org/eput/generate/handyfactsheetstoppingantidepressantsuk.pdf

1.4.2 How to treat discontinuation symptoms?

If a person has withdrawal symptoms when they stop taking antidepressant medication or reduce their dose, reassure them that they are not having a relapse of their depression. Explain that:

- these symptoms are common
- relapse does not usually happen as soon as you stop taking an antidepressant medication or lower the dose
- even if they start taking an antidepressant medication again or increase their dose, the withdrawal symptoms may take a few days to disappear.

Mild symptoms – reassure patient, and monitor symptoms.

Severe symptoms – reintroduce the original medicine at the effective dose, or prescribe a medicine in the same class with a longer half-life (e.g. if patient was using paroxetine, introduce fluoxetine), withdraw slowly and monitor.[1]

	MAOI's	TCA's	SSRI's & related
Symptoms	**Common:** Agitation, irritability, ataxia, movement disorders, insomnia, somnolence, vivid dreams, cognitive impairment, slowed speech, pressured speech. **Occasionally:** Hallucinations, paranoid delusions.	**Common:** Flu-like symptoms (chills, fever, sweating, headache, nausea), insomnia, vivid dreams. **Occasionally:** Movement disorders, mania, cardiac arrhythmia.	**Common:** Flu-like symptoms, 'shock-like' sensations, dizziness, insomnia, vivid dreams, irritability, crying spells. **Occasionally:** Movement disorders, impaired concentration and memory.
Medicines most often associated with dis-continuation symptoms	All (Tranylcypromine is partly metabolised to amphetamine and is associated with a true 'withdrawal syndrome')	Amitriptyline Imipramine	Paroxetine (all SSRIs have the propensity to cause discontinuation syndrome) Venlafaxine (↑ risk of NMS), Duloxetine

References

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Annex 1

Licensed indication(s) for antidepressants

Medicine	Depression	Anxiety	OCD	Panic Disorder	Social Anxiety	PTSD	GAD	Bulimia - Nervosa	PMDD
Amitriptyline	✓								
Citalopram	✓			✓					
Clomipramine	✓		✓						
Dosulepin	✓								
Duloxetine	✓						✓		
Fluoxetine	✓		✓					✓	
Flupentixol	✓								
Imipramine	✓								
Lofepramine	✓								
MAOI's	✓								
Mianserin	✓								
Mirtazapine	✓								
Moclobemide	✓				✓				
Paroxetine	✓		✓	✓	✓	✓	✓		
Sertraline	✓		✓	✓	✓	✓			
Trazodone	✓	✓							
Venlafaxine	✓			✓	✓§		✓§		
Vortioxetine	✓								

Indications correct as of December 2015 – check for changes in the latest SPC.

Abbreviations

OCD = Obsessive Compulsive Disorder
PTSD = Post Traumatic Stress Disorder
GAD = Generalised Anxiety Disorder
PMDD = Pre-Menstrual Dysphoric Disorder

§ Only the XL formulation of Venlafaxine is licensed for these indications

References

1. Summary of Product Characteristics for Individual Medicines [accessed May 2017] http://www.medicines.org.uk/EMC/

Annex 2

Summary of Medicine Particulars (relative side effect profile)

Medicine[1]	Max Daily Dose (mg) Adult (Licensed)	Max Daily Dose (mg) Elderly (Licensed)	Relative Side Effects at Average Doses (mostly dose-related)						
			Anti-cholinergic	Cardiac	Nausea	Sedation	Over-dose Toxicity	Pro-convul sant	Sexual Dysfunct ion
Tricyclics (TCAs)									
Amitriptyline	200	75	+++	+++	++	+++	+++	++	++
Clomipramine	250	75	+++	++	++	++	+	++	+++
Dosulepin	150	75	++	++	0	+++	+++	++	++
Imipramine	300 (Hosp) 200 (Outpt)	50	++	++	++	+	+++	++	++
Lofepramine	210	<Ad	++	+	+	+	0	0	++
SSRIs									
Citalopram[2]	40	20	0	++	+++	0	+	0	++
Fluoxetine	60	60	0	0	++	0	0	0	++
Paroxetine	50(depression) 60 (others)	40	0	0	++	0	0	0	+++
Sertraline	200	200	0	0	++	0	0	0	++
Tricyclic-Related									
Mianserin	200 (usually30-90)	<Ad	+	0	0	+++	0	0	+
Trazodone	600 (Hosp) 300 (Outpt)	300	+	+	+++	++	+	0	++
MAOIs									
Isocarboxazid	60 (4-6weeks) then 40	10	++	++	++	0	++	0	+
Phenelzine	90	(90)	+	+	++	+	+++	0	+
Tranylcy-promine	30	(30)	+	+	++	+	+++	0	+
SNRIs									
Duloxetine	120	Caution	0	0	++	+	?	?	++
Venlafaxine	375 (tabs) 375 (SR caps)	375 (tabs) 375 (SR caps)	0	++	++	+	++	+	++
Others									
Flupentixol	3	1.5	++	0	0	+	+	?	+
Mirtazapine	45	45	0	0	0	++	0	++	++
Moclobemide	600	600	+	0	+	0	0	?	+

Key

+++ = Marked effect ++ = Moderate effect + = Mild effect 0 = Little effect

? = Unknown <Ad = Less than Adult dose NR = Not Recommended

References

1. Psychotropic Drug Directory 2014, Bazire S., Page Bros Ltd
2. MHRA Drug Safety Update, Volume 5, No 5, December 2011