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Antidepressants

There are many antidepressants to choose from and this bulletin provides information to support the evidence-based, safe and cost-effective choice of antidepressants to treat depression. Antidepressant use for non-depression mental health disorders or pain management is outside of the scope of this bulletin. Concerns have been raised over an increase in antidepressant prescribing. Guidance is provided on the prescribing, review and monitoring of antidepressant therapy for the treatment of depression.

£276.9 million is spent annually on the prescribing of antidepressant medication in England, Wales, Isle of Man and Scotland (NHSBSA (May 22 to April 23), Public Health Scotland (April 22 to March 23).

Recommendations

- Antidepressant medication is not routinely recommended as first-line treatment for less severe depression (scoring less than 16 on the Patient Health Questionnaire (PHQ-9) scale), unless that is the person's preference.
  - » First-line options include non-pharmacological therapy, e.g. cognitive behavioural therapy (CBT).
  - » If a person's preference is an antidepressant, Selective Serotonin Reuptake Inhibitors (SSRIs) are recommended as a treatment option for people with less severe depression.
- Treatment options for a new episode of more severe depression (scoring 16 or more on the PHQ-9 scale) include a combination of individual CBT and an antidepressant. This can be an SSRI, Serotonin Noradrenaline Reuptake Inhibitor (SNRI), or other antidepressant if indicated based on previous clinical and treatment history.
- The choice of antidepressant should be based on the individual person's requirements, including the presence of concomitant disease, existing therapy, suicide risk, and previous response to antidepressant therapy.
- SSRIs are generally well tolerated, have a good safety profile and should be considered as the first choice for most people.
- Sertraline, escitalopram and mirtazapine compared with other antidepressants are less costly and have higher response and lower dropout rates for the acute treatment of adults with major depressive disorder. They should be considered for medicines formulary inclusion and as first choices in new patients where suitable for the individual.
- Be aware of contraindications, cautions, side effects and risk of interactions with antidepressants (especially for those on multiple medications for chronic physical health problems).
- Prescribe SSRIs with caution to people with a history of bleeding disorders (especially gastrointestinal (GI) bleeding).
  - » Do not normally offer SSRIs to people taking non-steroidal anti-inflammatory drugs (NSAIDs) due to the synergistic increased risk of GI bleeding.
  - » If there is no suitable alternative, an SSRI may be prescribed if a gastroprotective medicine is also offered.

Recommendations

- In coronary heart disease (CHD):
  - Do not prescribe citalopram and escitalopram to people with known QT interval prolongation, people with congenital long QT syndrome or with concurrent use of drugs known to prolong the QT interval.
  - Patients who currently take doses of citalopram and escitalopram that are higher than the recommended maximum daily doses should have their treatment reviewed. Maximum dose changes at age 65.
  - In people with unstable angina or who have had a recent myocardial infarction, sertraline has been shown to be safe.
  - SSRIs and mirtazapine are the preferred antidepressants in CHD.
  - Sertraline, fluoxetine, or paroxetine are the SSRIs of choice.
  - Consider gastroprotection in people taking aspirin and a SSRI.
  - Tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), duloxetine, reboxetine, and venlafaxine should be avoided if possible.
- Dosulepin should not be initiated in primary care for any new diagnosis and should be deprescribed where appropriate, see PrescQIPP Bulletin 310: Dosulepin.
- Trimipramine should not be initiated in primary care for any new diagnosis and should be deprescribed where appropriate, see PrescQIPP Bulletin 311: Trimipramine.
- When changing from one antidepressant to another, abrupt withdrawal should be avoided unless there has been a serious adverse event. Cross-tapering is preferred where possible.
- Patients should be counselled to continue treatment for at least six months after the remission of symptoms.
- In agreement with the patient, when stopping a person's antidepressant medication take into account the pharmacokinetic profile (for example, antidepressants with a short half-life such as paroxetine and venlafaxine, will need to be tapered more slowly) and the duration of treatment. Slowly reduce the dose to zero in a stepwise fashion, at each step prescribing a proportion of the previous dose.
- In England (and Wales, Northern Ireland and Scotland where appropriate), review and implement the five actions listed for Integrated Care Systems (ICSs) to optimise personalised care for adults prescribed medicines associated with dependence and withdrawal symptoms.

Background

Depression refers to a wide range of mental health problems characterised by the absence of a positive affect (a loss of interest and enjoyment in ordinary things and experiences), low mood and a range of associated emotional, cognitive, physical and behavioural symptoms.[1] In the fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5), major depressive disorder is defined as the presence of at least five defining symptoms, during the same two-week period, where at least one of the symptoms is depressed mood or loss of interest or pleasure.[1,2] The nine symptoms are:[1]

- Depressed mood – indicated by subjective report or observation by others.
- Loss of interest or pleasure in almost all activities – indicated by subjective report or observation by others.
- Significant (more than 5% in a month) unintentional weight loss or gain or decrease or increase in appetite.

- Sleep disturbance (insomnia or hypersomnia).
- Psychomotor changes (agitation or retardation) severe enough to be observable by others.
- Tiredness, fatigue, or low energy, or decreased efficiency with which routine tasks are completed.
- A sense of worthlessness or excessive, inappropriate, or delusional guilt (not merely self-reproach or guilt about being sick).
- Impaired ability to think, concentrate, or make decisions – indicated by subjective report or observation by others.
- Recurrent thoughts of death (not just fear of dying), suicidal ideation, or suicide attempts.

In the International Classification of Diseases-11 (ICD-11), depression is defined as the presence of depressed mood or diminished interest in activities occurring most of the day, nearly every day, for at least 2 weeks, accompanied by other symptoms such as:[1]

- Reduced ability to concentrate and sustain attention or marked indecisiveness
- Beliefs of low self-worth or excessive or inappropriate guilt
- Hopelessness about the future
- Recurrent thoughts of death or suicidal ideation or evidence of attempted suicide
- Significantly disrupted sleep or excessive sleep
- Significant changes in appetite or weight
- Psychomotor agitation or retardation
- Reduced energy or fatigue

The NICE guideline - Depression in adults: treatment and management [NG222], defines people with chronic depressive symptoms as those who continually meet criteria for the diagnosis of a major depressive episode for at least two years, or have persistent subthreshold symptoms for at least two years, or who have persistent low mood with or without concurrent episodes of major depression for at least two years. People with depressive symptoms may also have a number of social and personal difficulties that contribute to the maintenance of their chronic depressive symptoms.[1]

The prevalence of depression varies in the literature, depending on the study population country and region, definitions of depression, and study methodology. There is a lack of large-scale longitudinal general population studies in the literature:

- The World Health Organization (WHO) states that depression is common and a leading cause of disability worldwide.[3]
- An international World Mental Health Survey Initiative epidemiological study of 'major depressive episode' in 2011 used population-based data from 18 countries (n = 89,037) and found:
  - The average lifetime prevalence estimate was 14.6% for adults in high-income countries.
  - The average 12-month prevalence estimate was 5.5% for adults in high-income countries.
  - The average age of onset was 25.7 years in adults in high-income countries.
  - The female-male ratio was about 2:1.
  - There were methodological limitations including sampling issues and variable response rates which affected data interpretation.[4]
- The Clinical Knowledge Summary (CKS) on depression highlights that expert opinion in a review article notes a peak in prevalence occurs in the second and third decades of life, with a subsequent smaller peak in the fifth and sixth decades.[2]

The underlying cause of depression is unknown but is likely to result from a complex interaction of genetic, environmental, biological, cultural, and psychological factors.[2]

Table 1: Risk factors for depression and risk factors for relapse of depression[2]

Risk factors for depression include:	
• Female sex	• Past history of depression
• Older age	• Family history of depressive illness or suicide
• Past history of depression	• History of other mental health conditions and/or substance misuse
• Personal, social, or environmental factors, such as relationship issues or breakdown, bereavement, stress, poverty, unemployment, homelessness, social isolation, or past history of child maltreatment	• Other chronic physical health conditions associated with functional impairment (such as diabetes mellitus, chronic obstructive pulmonary disease, cardiovascular disease, chronic pain syndromes, epilepsy, and stroke disease)
• Postpartum period	
Risk factors for relapse of depression include:	
• Older age of onset	• History of severe depression (including severe functional impairment)
• History of recurrent episodes of depression, particularly if frequent or within the past two years	• Other chronic physical or mental health conditions, especially in the elderly
• Incomplete response to previous treatment, including residual symptoms	• Ongoing personal, social, or environmental factors (see above)
• Unhelpful coping styles or behaviours, such as avoidance or rumination	

Depression severity exists along a continuum and is essentially composed of three elements:[1]

- Symptoms (which may vary in frequency and intensity).
- Duration of the disorder.
- The impact on personal and social functioning.

Severity of depression is therefore a consequence of the contribution of all of these elements. Traditionally, depression severity has been grouped under four categories (subthreshold, mild, moderate and severe) but the updated NICE guideline has defined new episodes of depression as less severe or more severe depression. Less severe depression encompasses subthreshold and mild depression, defined as depression scoring less than 16 on the Patient Health Questionnaire (PHQ-9) scale. More severe depression encompasses moderate and severe depression and is defined as depression scoring 16 or more on the PHQ-9 scale.[1]

The PHQ-9 scale is a depression questionnaire (attachment 1) which is validated for use in primary care. It is a nine-item, self-administered scale, which reflects the DSM-5 criteria. It classifies current symptoms on a scale of zero to three. The maximum score is 27. It can be downloaded free of charge from www.phqscreeners.com.[2]

The questionnaire asks – over the last two weeks, how often have you been bothered by any of the following problems?

- Little interest or pleasure in doing things.
- Feeling down, depressed, or hopeless.
- Trouble falling or staying asleep or sleeping too much.
- Feeling tired or having little energy.
- Poor appetite or overeating.
- Feeling bad about yourself — or that you are a failure or have let yourself or your family down.
- Trouble concentrating on things, such as reading the newspaper or watching television.
- Moving or speaking so slowly that other people could have noticed? Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual.
- Thoughts that you would be better off dead or of hurting yourself in some way.

The patient indicates their answer as - Not at all (score 0), Several days (score 1), More than half the days (score 2), Nearly every day (score 3).[5]

National guidance

NICE clinical guidelines cover the NHS in England, Wales and Northern Ireland. The Scottish Intercollegiate Guidelines Network (SIGN) produces clinical guidelines in Scotland.[6]

NICE guideline Depression in adults: treatment and management [NG222] covers identifying, treating and managing depression in people aged 18 and over. It recommends treatments for first episodes of depression, further-line treatments, and provides advice on preventing relapse and managing chronic depression, psychotic depression and depression with a coexisting diagnosis of personality disorder.[1]

The guideline does not recommend that antidepressant medication is routinely offered as first-line treatment for less severe depression, unless that is the person's preference. NICE have a visual summary to guide and inform the conversation when discussing the treatment options available.[1]

SSRIs are recommended as a treatment option for less severe depression if an antidepressant medication is the person's preference. Treatment options for more severe depression can be a SSRI, SNRI or another antidepressant if indicated based on previous clinical and treatment history.[1]

NICE clinical guideline [CG91] Depression in adults with a chronic physical health problem: recognition and management covers identifying, treating and managing depression in people aged 18 and over who also have a chronic physical health problem such as cancer, heart disease or diabetes. It recommends that antidepressants are not routinely used to treat subthreshold depressive symptoms or mild depression in people with a chronic physical health problem (because the risk-benefit ratio is poor), but they should be considered for people with any of the following:[7]

- A past history of moderate or severe depression.
- Mild depression that complicates the care of the physical health problem.
- Initial presentation of subthreshold depressive symptoms that have been present for a long period (typically at least two years).
- Subthreshold depressive symptoms or mild depression that persist(s) after other interventions.

Depression in children and young people: identification and management [NG134] covers identifying and managing depression in children and young people aged 5 to 18 years. This guideline recommends that antidepressant medication should not be used for the initial treatment of mild depression and should not be offered to a child or young person with moderate to severe depression except in combination

with a concurrent psychological therapy. If an antidepressant is to be prescribed this should only be following an assessment and diagnosis by a child and adolescent psychiatrist. When an antidepressant is prescribed to a child or young person with moderate to severe depression, it should be fluoxetine as this is the only antidepressant for which clinical trial evidence shows that the benefits outweigh the risks, however use of fluoxetine in children under the age of 8 years is off-label. If treatment with fluoxetine is unsuccessful or is not tolerated because of side effects, sertraline or citalopram are the recommended second-line treatments (off-label use in under 18). Paroxetine, venlafaxine, tricyclic antidepressants (TCAs) and St John's Wort should not be used for the treatment of depression in children and young people. There are no trials for St John's Wort in children or young people, it has an unknown side-effect profile and is known to interact with a number of other drugs, including contraceptives, therefore St John's Wort should not be prescribed. A child or young person prescribed an antidepressant should be closely monitored for the appearance of suicidal behaviour, self-harm or hostility, particularly at the beginning of treatment.[8-11]

For people with depression who also have learning disabilities, the NICE guideline on Mental health problems in people with learning disabilities: prevention, assessment and management recommends considering cognitive behavioural therapy, adapted for people with learning disabilities to treat depression or subthreshold depressive symptoms in people with milder learning disabilities.[12]

The NICE guideline for Autism spectrum disorder in adults: diagnosis and management states do not use antidepressant medication for the routine management of core features of autism in adults.[13]

The NICE guideline on Dementia: assessment, management and support for people living with dementia and their carers recommends considering psychological treatments for people living with mild to moderate dementia who have mild to moderate depression and/or anxiety. The guidelines state do not routinely offer antidepressants to manage mild to moderate depression in people living with mild to moderate dementia, unless they are indicated for a pre-existing severe mental health problem.[14]

For people with depression who are menopausal, the NICE guideline Menopause: diagnosis and management states that menopausal women and healthcare professionals involved in their care should understand that there is no clear evidence for SSRIs or SNRIs to ease low mood in menopausal women who have not been diagnosed with depression.[15]

NICE clinical guidance Antenatal and postnatal mental health: clinical management and service guidance [CG192] recommends when choosing a TCA, SSRI or SNRI, (off-label use) the prescriber should consider the following:[16]

- Previous response to these drugs.
- The stage of pregnancy.
- What is known about the reproductive safety of these drugs.
- The uncertainty about whether any increased risk to the foetus and other problems for the woman or baby can be attributed directly to these drugs or may be caused by other factors.
- The risk of discontinuation symptoms in the woman and neonatal adaptation syndrome in the baby with most TCAs, SSRIs and SNRIs, in particular paroxetine and venlafaxine.
- When assessing the risks and benefits of TCAs, SSRIs or SNRIs for a woman who is considering breastfeeding, take into account:
  - the benefits of breastfeeding for the woman and baby
  - the uncertainty about the safety of these drugs for the breastfeeding baby
  - the risks associated with switching from or stopping a previously effective medication
  - seek advice from a specialist (preferably from a specialist perinatal mental health service) if there is uncertainty about specific drugs.

Also see the section on safety below for more information on SSRIs and SNRIs in pregnancy.

The NICE guideline [NG215] about Medicines associated with dependence or withdrawal symptoms: safe prescribing and withdrawal management for adults covers general principles for prescribing and managing withdrawal from dependence-forming medicines and antidepressants in primary and secondary care.[17]

In March 2023 NHS England published Optimising personalised care for adults prescribed medicines associated with dependence or withdrawal symptoms: Framework for action for Integrated Care Boards (ICBs) and primary care to support people who are taking medicines associated with dependence and withdrawal symptoms. Five actions are listed for ICSs:[18]

Action 1 – Personalised care and shared decision-making

Person-centred care should be embedded in service specifications and development plans to provide opportunities for healthcare professionals to practise personalised care, e.g. in dedicated clinics or using structured medication reviews (SMRs), where the clinician is working within their competence. During regular medication reviews and when considering prescribing, healthcare professionals should openly discuss with the patient (with consideration for their health literacy): the intended outcome from prescribing; potential benefits, risk and harm of the treatment; decisions about whether to continue, stop or taper treatment.

Action 2 – Alternative interventions to medicines

Prescribers should offer alternative interventions and services, where appropriate, to patients when a prescription for a medicine associated with dependence and withdrawal symptoms is first considered, or when the prescription is reviewed. ICSs should ensure that alternative treatment options are available and that prescribers are aware of them.

Action 3 – Service specification and change management

ICSs task and finish groups (or similar) should ensure appropriate commissioning of services for patients taking medicines associated with dependence or withdrawal symptoms, including services for patients wishing to reduce or stop these medicines. Additionally, ensure that people with a role in service design, provision, monitoring and implementation have access to sufficient education and training on medicines associated with dependence and withdrawal symptoms, so they can meet their population's needs.

Action 4 – Taking whole system approaches

A whole system approach and pathways involving multiple interventions should be used to improve care for people prescribed medicines associated with dependence and withdrawal symptoms. A service specification should set out the requirements for any commissioned services and should be produced in collaboration with other partners, including local authorities and third sector bodies. Service specifications to include such things as:

- Appropriate services for patients experiencing withdrawal symptoms from deprescribing of these medicines.
- Alternative treatments and services for prescribers to offer the right type and level of support for patients.
- A requirement to deliver local care using multidisciplinary teams.
- A requirement to use data on prescribing and localised health inequalities.

Action 5 – Population health management

Primary care data on prescribing and localised health inequalities should be used to:

- Monitor access to services, patient experience and outcomes for communities within the ICSs that often experience health inequalities.
- Help local areas prioritise.

- Identify key lines of enquiry.
- Inform action plans that prioritise and support patients at greatest risk of dependence and withdrawal.

ICSs should ensure that processes are in place to identify and review medicines of patients who may have been taking them for longer than the evidence suggests is helpful.

The NICE [TA367] recommends vortioxetine as an option for treating major depressive episodes in adults whose condition has responded inadequately to two antidepressants within the current episode. The NICE Appraisal Committee concluded that no convincing evidence existed to show that vortioxetine was more or less effective than other antidepressants. The Committee noted that the company considered vortioxetine innovative because: it reduces cognitive dysfunction, it minimises impact on social relationships, and it reduces symptoms associated with stopping treatment.[19]

NICE is unable to recommend the use in the NHS of agomelatine for the treatment of major depressive episodes because no evidence submission was received from the manufacturer or sponsor of the technology. NICE [TA231] was terminated as the manufacturer of agomelatine (Servier) drew attention to the fact that NICE guidelines for England and Wales recommend generic SSRIs as first-line treatment followed by a different SSRI or a better tolerated newer-generation agent as second-line treatment. The manufacturer noted that the majority of the clinical trial evidence for agomelatine was as a first-line treatment and furthermore was not against the full range of comparators in the scope. The manufacturer stated that this precluded the development of an economic case that would address the NICE decision problem and maintain the requisite level of certainty.[20]

NICE [TA854] does not recommend esketamine nasal spray with a SSRI or a SNRI, within its marketing authorisation, for treatment-resistant depression that has not responded to at least two different antidepressants in the current moderate to severe depressive episode in adults. The company positioned esketamine nasal spray for people who have had at least three antidepressants before, with or without another treatment like lithium or an antipsychotic medicine. This is narrower than the marketing authorisation, and also how clinical experts advised esketamine would likely be used in NHS practice. The clinical evidence at this positioning is uncertain because it only considers a small number of people from the full clinical trial population. But it suggests that for people who have had at least three antidepressants with or without another treatment, esketamine with an SSRI or SNRI is likely more effective than placebo with an SSRI or SNRI. Because the trials were short the long-term benefits of esketamine are uncertain. Also, the trial evidence excluded people with characteristics of depression like psychosis or recent suicidal ideation with intent. This limits how well the evidence applies to the NHS, because people having treatment for depression in the NHS may have psychosis or recent suicidal ideation with intent. As esketamine is unlikely to be an acceptable use of NHS resources, it is not recommended.[21]

The Scottish Intercollegiate Guidelines Network currently do not have guidance on the pharmaceutical management of depression.[22]

The British Association for Psychopharmacology (BAP) guidelines states that the choice of antidepressant drug should be matched to individual person requirements as far as possible, taking into account likely short-term and long-term effects. In the absence of special factors, antidepressants that are better tolerated and safer in overdose should be chosen. There is most evidence for SSRIs which, together with other newer antidepressants, are first line choices. Older TCAs should generally be reserved for situations when first-line drug treatment has failed. Older monoamine oxidase inhibitors (MAOIs) should generally be reserved for people where first-line antidepressant therapy has not been effective and should only be initiated by practitioners with expertise in treating mood disorders.[23]

NICE guidance recommended treatments

Make a shared decision with the person about their treatment and involve family members, carers or other supporters if agreed. Discuss:[1]

- What, if anything, they think might be contributing to the development of their depression.
- Whether they have ideas or preferences about starting treatment, and what treatment options they have previously found helpful or might prefer.
- Their experience of any prior episodes of depression, or treatments for depression.
- What they hope to gain from treatment.

Discuss with people with depression their preferences for treatments (including declining an offer of treatment, or changing their mind once a treatment has started) by providing:[1]

- Information on what treatments are NICE recommended, their potential benefits and harms, any waiting times for treatments, and the expected outcomes.
  - » Treatment for a new episode of less severe depression
  - » Treatment for a new episode of more severe depression
- A choice of:
  - » The treatments recommended in this guideline.
  - » How they will be delivered (for example individual or group, in person or remotely) and
  - » Where they will be delivered.
- The option to attend with a family member or friend, when possible, for some or all their treatment.
- The option to express a preference for the gender of the healthcare professional, to see a professional they already have a good relationship with, or to change professional if the relationship is not working.

Treatment for a new episode of less severe depression (scoring less than 16 on the PHQ-9 scale)

For people with less severe depression who do not want treatment, or people who feel that their depressive symptoms are improving use active monitoring:[1]

- Discuss the presenting problem(s), any underlying vulnerabilities and risk factors, as well as any concerns that the person may have.
- Make sure the person knows they can change their mind and how to seek help.
- Provide information about the nature and course of depression.
- Arrange a further assessment, normally within two to four weeks.
- Make contact (with repeated attempts if necessary), if the person does not attend follow-up appointments.

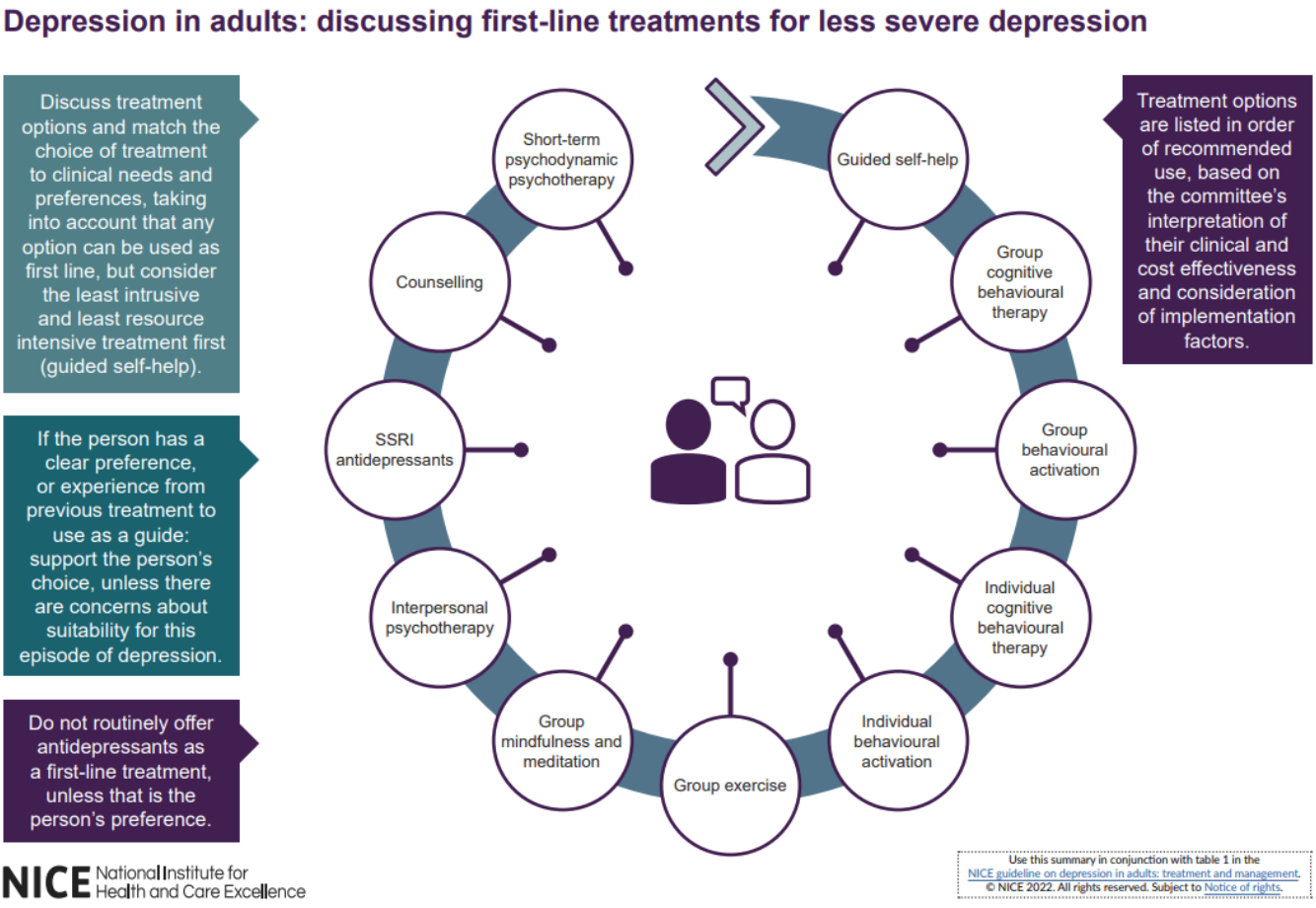
Treatment options for a new episode of less severe depression in order of the NICE committee's interpretation of their clinical and cost effectiveness and consideration of implementation factors are:[1]

- Guided self-help – Including structured cognitive behavioural therapy (CBT), structured behavioural activation (BA), problem solving or psychoeducation materials. These can be delivered in person, by telephone, or online.
- Group CBT
- Group BA
- Individual CBT

- Individual BA
- Group exercise
- Group mindfulness and meditation
- Interpersonal psychotherapy (IPT)
- SSRI antidepressants
- Counselling
- Short-term psychodynamic psychotherapy (STPP)

CBT is a range of talking therapies based on the theory that thoughts, feelings, what we do and how our body feels are all connected. If we change one of these, we can alter the others. When people feel low or upset, they can often fall into patterns of thinking and responding which can worsen how they feel. CBT works to help people notice and change problematic thinking styles or behaviour patterns so they can feel better.[24]

Use the visual summary to guide and inform the conversation and take into account that all treatments can be used as first-line treatments, but consider the least intrusive and least resource intensive treatment first (guided self-help).[1]



Treatment for a new episode of more severe depression (scoring more than 16 on the PHQ-9 scale)

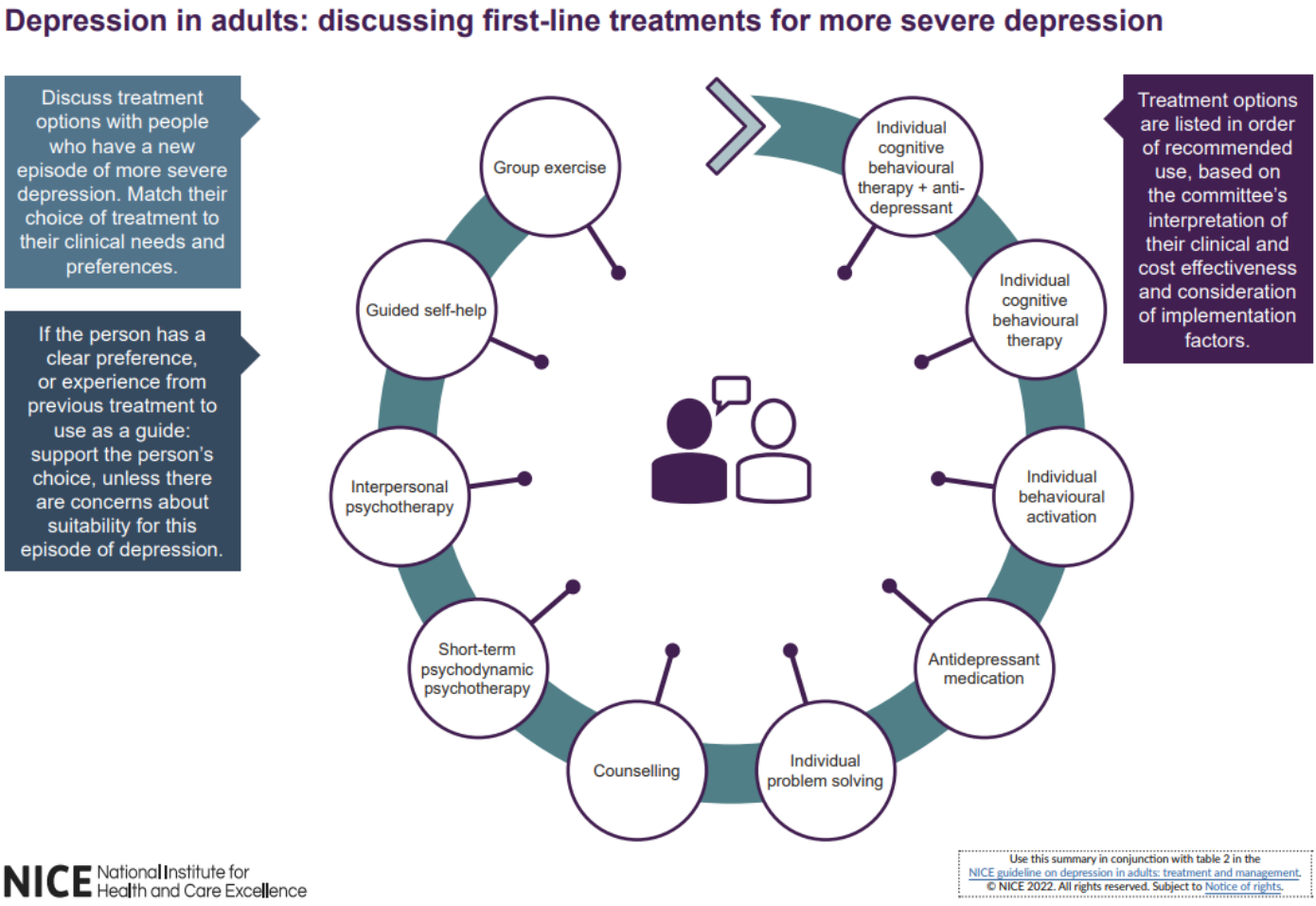
Treatment options for a new episode of more severe depression in order of the committee's interpretation of their clinical and cost effectiveness and consideration of implementation factors are:[1]

- Combination of individual CBT and an antidepressant
- Individual CBT

- Individual BA
- Antidepressant medication
- Individual problem-solving
- Counselling
- STPP
- IPT
- Guided self-help
- Group exercise

Antidepressant medication for more severe depression can be an SSRI, SNRI, or other antidepressant if indicated based on previous clinical and treatment history. SSRIs are generally well tolerated, have a good safety profile and should be considered as the first choice for most people. Of the TCAs, lofepramine has the best safety profile[1] as it is the least dangerous in overdose.

Use the visual summary to guide and inform the conversation and take into account that all treatments can be used as first-line treatments.[1]



For both less severe and more severe depression antidepressant medication is usually taken for at least six months including after symptoms remit for less severe and severe depression. Benefits should be felt within four weeks.[1] If a person's depression has not responded after four weeks of antidepressant medication further-line treatment options should be discussed (see below).

A list of self-help resources for support is available in attachment 2. This includes a table for local contacts which can be adapted for use. Attachment 3 provides information on websites and apps for depression.

Further-line treatment options

If a person's depression has not responded at all after four weeks of antidepressant medication at a recognised therapeutic dose, or after four to six weeks for psychological therapy or combined medication and psychological therapy, discuss with them:[1]

- Any personal, social or environmental factors or physical or other mental health conditions that might explain why the treatment is not working.
- Whether they have had problems adhering to the treatment plan.

If any of these are the case, make a shared decision on how to address any problems raised. If a person's depression has not responded to treatment after addressing any problems raised and allowing adequate time for treatment changes to work, review the diagnosis and consider the possibility of alternative or comorbid conditions that may limit response to depression treatments. Provide reassurance that other treatments can be tried and may be effective.[1]

Table 2: Further-line treatment options[1]

If a person's depression has had no or a limited response to treatment with psychological therapy alone
Consider: • Switching to an alternative psychological treatment. • Adding an SSRI to the psychological therapy. • Switching to an SSRI alone.
If a person's depression has had no or a limited response to treatment with antidepressant medication alone
Consider: • Adding a group exercise intervention. • Switching to a psychological therapy (see treatment options for more severe depression). • Continuing antidepressant therapy by either increasing the dose or changing the drug. For example, by: » Increasing the dose of the current medication. » Switching to another medication in the same class (for example, another SSRI). » Switching to a medication of a different class, for example o an SSRI, SNRI in primary care, or in secondary care, a TCA or MAOI. o cross-tapering is needed see switching antidepressants where possible. » Switching to or from an MAOI, or from one MAOI to another, will need to take place in, or with advice from, secondary care. » TCAs are dangerous in overdose, although lofepramine has the best safety profile. • Changing to a combination of psychological therapy (for example, CBT, IPT or STPP) and medication.

If a person's depression has had no or a limited response to treatment with a combination of antidepressant medication and psychological therapy
Consider: • Switching to another psychological therapy. • Increasing the dose or switching to another antidepressant. • Adding in another medication.
Only consider vortioxetine when there has been no or limited response to at least two previous antidepressants.
Explain the possible increase in their side-effect burden. If they are willing to accept the possibility of an increased side-effect burden consider referral to a specialist mental health setting or consulting a specialist. Treatment options include: • 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).

Attachment 4 is a summary of the NICE recommended treatments.

Antidepressant initiation and review

When offering a person medication for the treatment of depression, discuss and agree a management plan with the person. Include:[1]

- The reasons for offering medication.
- The choices of medication (if a number of different antidepressants are suitable).
- The dose, and how the dose may need to be adjusted.
- The benefits, covering what improvements the person would like to see in their life and how the medication may help.
- The harms, covering both the possible side effects and withdrawal effects, including any side effects they would particularly like to avoid (for example, weight gain, sedation, effects on sexual function). Some commonly used antidepressants such as paroxetine and venlafaxine, are more likely to be associated with withdrawal symptoms, so particular care is needed with them.
- Any concerns they have about taking or stopping the medication.

Starting doses

Prescribe the starting dose of an antidepressant and titrate up to the recognised minimum effective dose.[25] See table 3 for starting doses, minimum effective doses and maximum doses.[2]

Table 3: Recommended starting doses, minimum effective doses, and maximum doses of antidepressants.[2,26]

Antidepressant	Daily starting dose	Usual minimum effective daily dose	Maximum daily dose for depression
SSRIs – starting doses are often effective and up-titration may not be necessary. However, where dose increases are considered appropriate, review in 4 weeks to assess efficacy, tolerance and acceptability			
Citalopram	20mg	20mg	40mg 20mg in >65 yrs and people with mild to moderate hepatic impairment
Escitalopram	10mg 5mg in >65 yrs and people with reduced hepatic function	10mg	20mg 10mg in >65 yrs and people with mild to moderate hepatic impairment
Fluoxetine	20mg	20mg	60mg
Fluvoxamine	50mg	50mg	300mg
Paroxetine	20mg	20mg	50mg 40mg in >65 yrs
Sertraline	50mg	50mg	200mg
TCAs – If people show a clear clinical response to a low-dose TCA, this dose may be maintained without further dose increases, providing the person maintains symptom improvement			
Imipramine	75mg 10mg in the elderly	At least 75mg-100mg* (possibly 125mg)	150-200mg
Lofepramine	140mg	140mg	210mg
Others – for mirtazapine, reboxetine, and venlafaxine starting doses are often effective and up-titration may not be necessary			
Duloxetine	60mg	60mg	60mg
Mirtazapine	15-30mg	30mg	45mg
Reboxetine	8mg	8mg	12mg
Trazodone	150mg 100mg in the elderly	150mg	300mg
Venlafaxine	75mg	75mg	375mg
Vortioxetine	10mg 5mg in the elderly	10mg	20mg

*Lower doses may be effective

See attachment 5 for more information on initiation and review of antidepressants.

Points to consider when prescribing

- SSRIs should be considered as the first choice of antidepressant treatment as they are well tolerated and have a good safety profile.[26]

  - » If a person has a new episode of less severe depression and wishes to start an antidepressant treatment offer a SSRI first-line.[2,26]
  - » If a person has a new episode of more severe depression and wishes to start an antidepressant treatment offer an SSRI or SNRI first-line.[2]
- Consider using sertraline or citalopram because they have less propensity for interactions.[7]
- SSRIs are less sedating and have fewer antimuscarinic and cardiotoxic effects than TCAs.[26]
- In people with unstable angina or who have had a recent myocardial infarction, sertraline has been shown to be safe.[26]
- Hyponatraemia (usually in the elderly) has been reported more frequently with SSRIs than with other antidepressants.[26]
- Hyponatraemia should be considered in all people who develop drowsiness, confusion, or convulsions while taking an antidepressant.[26]
- Do not prescribe citalopram and escitalopram to people with known QT interval prolongation, people with congenital long QT syndrome or with concurrent use of drugs known to prolong the QT interval.[2]
- Prescribe SSRIs with caution to people with a history of bleeding disorders (especially gastrointestinal bleeding).[2]
- Do not normally offer SSRIs to people taking non-steroidal anti-inflammatory drugs (NSAIDs) because of the increased risk of gastrointestinal bleeding.[7]
- If no suitable alternative antidepressant can be identified, SSRIs may be prescribed at the same time as NSAIDs if gastroprotective medicines (e.g. proton-pump inhibitors) are also offered.[7]
- Do not normally offer SSRIs to patients taking warfarin or heparin because of their anti-platelet effect.[7]
- Consider the risk of toxicity of the antidepressant in overdose.[7]
- Venlafaxine has a greater risk of death in overdose than SSRIs.[7]
- TCAs and MAOIs have the highest toxicity in overdose.[2]
- TCAs have potentially fatal cardiovascular effects (tachycardia, postural hypotension, slowed cardiac conduction) when taken in overdose. Overdose can also cause sedation, coma, and seizures.[2]
- The National Poisons Information Service (NPIS) is the service to which frontline NHS staff turn for advice on the diagnosis, treatment and care of patients who have been – or may have been – poisoned, either by accident or intentionally. Healthcare professionals with an enquiry please visit www.TOXBASE.org
- Limited quantities of TCAs should be prescribed at any one time because their cardiovascular and epileptogenic effects are dangerous in overdosage.[26]
- TCAs have similar efficacy to SSRIs but are more likely to be discontinued because of side-effects.[26]
- Among TCAs, dosulepin has particularly high toxicity, while lofepramine has relatively low toxicity.[2]
- Do not routinely start treatment with TCAs, except lofepramine, as they are associated with the greatest risk in overdose.[1]
- Dosulepin should not be initiated in primary care for any new diagnosis and should be deprescribed where appropriate, see PrescQIPP Bulletin 310: Dosulepin.[27]
- Trimipramine should not be initiated in primary care for any new diagnosis and should be deprescribed where appropriate, see PrescQIPP Bulletin 311: Trimipramine.[27]

- MAOIs, combined antidepressants and lithium augmentation of antidepressants should normally only be prescribed by specialist mental health professionals.[7]
- MAOIs have dangerous interactions with some foods.[26]
- Moclobemide (MAOI) prolongs the QT interval and toxic effects in overdose may include hypertensive crisis, serotonin and noradrenaline toxicity, agitation, aggressiveness, and behavioural changes.[2]
- The combination of an SSRI, SNRI or TCA with a MAOI is potentially dangerous and should be avoided.[1]
- Although there is evidence that St John's Wort may be of benefit in less severe depression, healthcare professionals should:
  - Advise people with depression of the different potencies of the preparations available and of the potential serious interactions of St John's Wort with other drugs.[1] Interactions with St John's Wort are listed in the BNF.[26] MIND has some useful patient resources on St John's Wort available at www.mind.org.uk
  - 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 hormonal contraceptives, anticoagulants and anticonvulsants).[1]
  - Check if patient is taking St John's Wort.
- There is marked inter-individual variation in tolerability which is not easily predicted by knowledge of a drug's likely adverse effects. A flexible approach is usually required to find the right drug for a particular person.[28]

Management

The first review will usually be within two weeks to check that symptoms are improving and for side effects, or after one week if a new prescription is for a person aged 18 to 25 years or if there is a particular concern for risk of suicide.[1]

Treatment should be continued for at least four weeks (six weeks in the elderly) before considering whether to switch antidepressant due to lack of efficacy. In cases of a partial response, continue for a further two to four weeks (elderly people may take longer to respond).[26]

Following remission, antidepressant treatment should be continued at the same dose for at least six months (about twelve months in the elderly), but should be reviewed regularly.[1,26]

Preventing relapse

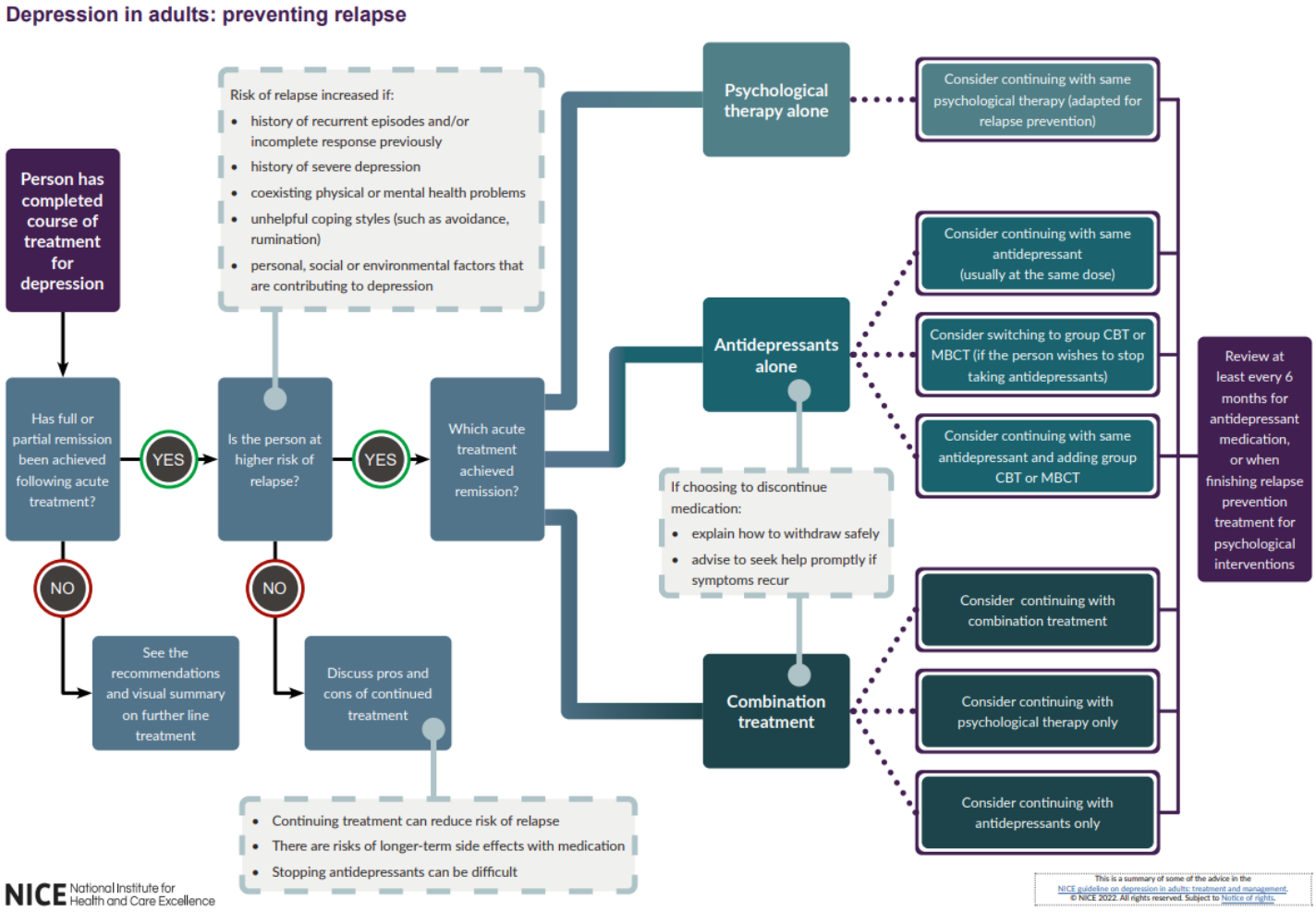
Discuss with people that continuation of treatment (antidepressants or psychological therapies) after full or partial remission may reduce their risk of relapse and may help them stay well. Reach a shared decision on whether or not to continue a treatment for depression based on their clinical needs and preferences. Use the visual summary on preventing relapse to guide and inform the conversation.[1]

Discuss with people the potential risks of continuing with antidepressants long term, and how these balance against the risks of depression relapse. The risks include possible side effects, such as an increased bleeding risk or long-term effects on sexual function and difficulty stopping antidepressants.[1]

Review treatment for people continuing with antidepressant medication to prevent relapse at least every six months. At each review:

- Monitor their mood.
- Review any side effects.

- Review any medical, personal, social or environmental factors that may affect their risk of relapse and encourage them to access help from other agencies.
- Discuss with them if they wish to continue treatment, or if they wish to stop antidepressant treatment. (See section on stopping antidepressant medication.)[1]



Clinical effectiveness

There is little to choose between the different classes of antidepressant drugs in terms of efficacy, so choice should be based on the individual person's requirements, including the presence of concomitant disease, existing therapy, suicide risk, and previous response to antidepressant therapy. During the first few weeks of treatment, there is an increased potential for agitation, anxiety, and suicidal ideation.[26]

Cipriani et al published a systematic review and meta-analysis of placebo-controlled and head-to-head trials of 21 antidepressants used for the acute treatment of adults (≥18 years old and of both sexes) with major depressive disorder in 2018. The review included 522 trials comprising 116,477 participants randomly assigned to 21 individual first-generation and second-generation antidepressant drugs or placebo. Primary outcomes were efficacy (response rate) and acceptability (treatment discontinuations due to any cause).[28]

In terms of efficacy, all antidepressants were more effective than placebo, with odds ratios (ORs) ranging between 2.13 (95% credible interval [CrI] 1.89–2.41) for amitriptyline and 1·37 (1.16–1.63) for reboxetine. For acceptability, only agomelatine (OR 0.84, 95% CrI 0.72–0.97) and fluoxetine (0.88, 0.80–0.96) were associated with fewer dropouts than placebo, whereas clomipramine was worse than placebo (1.30, 1.01–1.68). Forty six (9%) of 522 trials were rated as high risk of bias, 380 (73%) trials as moderate, and 96 (18%) as low; and the certainty of evidence was moderate to very low.[28]

Table 4: Comparison of antidepressant efficacy and tolerability from head-to-head studies[28]

More effective	More tolerable	Higher response and lower dropout rates
• Agomelatine • Amitriptyline • Escitalopram • Mirtazapine • Paroxetine • Venlafaxine • Vortioxetine	• Agomelatine • Citalopram • Escitalopram • Fluoxetine • Sertraline • Vortioxetine	• Agomelatine • Escitalopram • Mirtazapine • Paroxetine • Sertraline
Less effective	**Less tolerable**	**Lower response and higher dropout rates**
• Fluoxetine • Fluvoxamine • Reboxetine • Trazodone	• Amitriptyline • Clomipramine • Duloxetine • Fluvoxamine • Reboxetine • Trazodone • Venlafaxine	• Fluvoxamine • Reboxetine • Trazodone

These findings may be of assistance when choosing between antidepressants for formulary inclusion or the treatment of individual people. However, the authors acknowledge that some antidepressant adverse effects occur over a prolonged period and so the positive results need to be used with caution given the short duration of the trials included in the meta-analysis. Also, given the modest effect size, non-response to antidepressants will occur and their findings can only guide first step choices. They acknowledge that they did not do a formal cost-effective analysis, but all the most effective antidepressants they found are now off patent and available in generic form.[28]

A systematic review and random-effects model network meta-analysis compared the efficacy, acceptability, tolerability, and safety of antidepressants to treat adults with major depressive disorder in the maintenance phase. The meta-analysis comprised 34 studies and 20 antidepressants (n = 9,384, mean age = 43.8 years, and 68.1% females). In terms of the six month relapse rate (primary outcome, efficacy), amitriptyline, citalopram, duloxetine, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, reboxetine, sertraline, venlafaxine, and vortioxetine outperformed placebo. Compared with placebo, paroxetine, sertraline, venlafaxine, and vortioxetine had lower all-cause discontinuation; however, sertraline had a higher discontinuation rate due to adverse events. Compared with placebo, sertraline and vortioxetine were associated with a higher incidence of nausea/vomiting. In conclusion, paroxetine, venlafaxine, and vortioxetine had reasonable efficacy, acceptability, and tolerability in the treatment of adults with stable major depressive disorder.[29]

A systematic review to assess SSRI monotherapy dose-response effects for the treatment of depression in adults (age ≥18 years) reporting efficacy, acceptability, or tolerability found that SSRIs demonstrated flat dose-response effects; and standard doses were optimal for efficacy. Standard daily doses were defined as 20mg for citalopram, fluoxetine, paroxetine; 50mg for sertraline; and 10mg for escitalopram. Higher than standard daily doses were associated with higher dropout rates and a greater incidence of adverse drug effects (e.g. nausea, sexual dysfunction, fatigue, anxiety).[30]

Safety

Be aware of contraindications, cautions, side effects and risk of interactions with antidepressants (especially for those on multiple medications for chronic physical health problems). Refer to the BNF and Summary of product characteristics (SPCs) for advice.

Citalopram, escitalopram and QT interval

Citalopram and escitalopram cause QT interval prolongation and may have an additive effect to other drugs that prolong the QT interval so co-administration is contraindicated. These include:[31]

- Class IA and III antiarrhythmics (e.g. amiodarone, dronedarone, quinidine).
- Antipsychotics (e.g. phenothiazine derivatives, pimozide, haloperidol).
- TCAs.
- Some antimicrobial agents (e.g. sparfloxacin, moxifloxacin, erythromycin IV, pentamidine, antimalaria treatment—particularly halofantrine).
- Some antihistamines (astemizole, mizolastine).
- Some antiretrovirals (e.g. ritonavir, saquinavir, lopinavir).

People taking concomitant medications (e.g. some antiretroviral medications, omeprazole and cimetidine) known to increase plasma levels of escitalopram and citalopram may require a dose reduction in light of these most recent QT data.[31]

The effect of citalopram and escitalopram on QT interval prolongation is dose dependant. Elderly people have a higher exposure due to age-related decline in metabolism and elimination. The maximum dose of both medicines has therefore been restricted in people older than 65 years.[31] Patients who currently take doses of citalopram and escitalopram that are higher than the recommended maximum daily doses should have their treatment reviewed.

Table 5: Maximum daily doses of citalopram and escitalopram[31]

	Adults	Adults >65 years	Adults with hepatic impairment
Citalopram	40mg	20mg	20mg
Escitalopram	20mg	10mg	10mg

Monitoring recommendations for citalopram and escitalopram are:[31]

- In people with cardiac disease, an ECG review should be considered before treatment with citalopram and escitalopram.
- Electrolyte disturbances (e.g. hypokalaemia and hypomagnesaemia) should be corrected before treatment with citalopram and escitalopram. Monitoring of serum magnesium is advised, particularly in elderly people, who may be taking diuretics or proton pump inhibitors.
- If cardiovascular symptoms, such as palpitations, vertigo, syncope, or seizures develop during treatment, cardiac evaluation including an ECG should be undertaken to exclude a possible malignant cardiac arrhythmia.
- If QTc interval is >500 milliseconds, treatment should be withdrawn gradually.
- If QTc interval duration is between 480 milliseconds and 500 milliseconds, the balance of benefits and risks of continued treatment should be carefully considered, alongside options for dose reduction or gradual withdrawal.

Risk of fractures with SSRIs and TCAs

A review of nine epidemiological studies, mainly in people aged 50 years or older, shows an increased risk of bone fractures in people receiving SSRIs and TCAs. The range of odds ratios for fractures associated with current use of SSRIs (irrespective of dose or duration of use) is between 1.4 (95% CI 0.93–2.24) and 2.4 (2.0–2.7). These risks were significant in most studies. The odds ratios for studies that included TCAs varied between 1.2 (0.7–2.2) and 2.2 (1.8–2.8), and in all but one study was lower than the estimates for SSRIs. Six of the nine studies assessed dose response and observed a trend more consistently for SSRIs compared with TCAs. Six of the nine studies assessed duration of use and found that the risk of fracture associated with SSRIs seems to increase initially to a peak within the first 6-12 months; risk subsequently decreases but remains elevated with prolonged use (>1.5 years). Risk with TCAs peaks shortly after initiation (1-2 months) and disappears after prolonged use (>6-12 months). The persistence of the effect after cessation of use was assessed in four of the nine studies. The increased risk observed for SSRIs and TCAs disappears relatively shortly after discontinuation (3-12 months). None of the studies investigated the effects of dose and duration simultaneously. The mechanism leading to this increased risk is unclear. Healthcare professionals should be aware of epidemiological data showing a small increased risk of fractures associated with the use of TCAs and SSRIs and should take this risk into account in their discussions with people and in prescribing decisions.[32]

SSRIs and SNRIs in pregnancy

Epidemiological evidence suggests a possible small increased risk of congenital cardiac defects in association with fluoxetine in early pregnancy, similar to that seen with paroxetine. Epidemiological data from seven cohort studies provided a risk estimate of 1.08 (0.84–1.39) for all congenital malformations with fluoxetine use. Analysis of data from five studies out of the seven gave a risk estimate of 1.43 (0.83–2.47) for congenital cardiac defects (data are odds ratios and 95% confidence intervals). The results suggest that fluoxetine is not associated with a risk of non-cardiac defects, and that any increased risk of malformations appears to be driven by a possible excess cardiac risk. There are insufficient data to draw conclusions on whether there is a similar risk for other SSRIs. Potential risks should be considered in the context of the benefits of treatment.[33]

Epidemiological data suggest that the use of SSRIs in pregnancy, particularly in the later stages, may increase the risk of persistent pulmonary hypertension (PPHN) in the newborn. Healthcare professionals are encouraged to enquire about the use of SSRIs and SNRIs, particularly in women in the later stages of pregnancy. The observed risk was approximately five cases per 1000 pregnancies whereas the background rate in the general population is one to two cases of PPHN per 1000 pregnancies. Although there is no evidence for the association of PPHN to SNRI treatment, this potential risk cannot be ruled out taking into account the related mechanisms of action. PPHN presents as severe hypoxaemia due to pulmonary artery hypertension. Close observation of neonates exposed to SSRIs or SNRIs for signs of PPHN is recommended after birth.[34]

SSRIs and SNRIs are known to increase bleeding risks due to their effect on platelet function. Data from observational studies suggest that the use of SSRI and SNRI antidepressants during the month before delivery may result in a small increased risk of postpartum haemorrhage.

Prescribers should consider this risk in the context of an individual person's bleeding and thrombotic risk assessment during the peripartum period and the benefits of antidepressants for the person's mental health during this time.[35]

Paroxetine and fluoxetine interaction with tamoxifen

Tamoxifen is a selective oestrogen-receptor modulator indicated for palliative and adjuvant treatment of oestrogen-receptor-positive breast cancer in premenopausal and postmenopausal women. Tamoxifen is a prodrug, and the formation of the active metabolite, endoxifen, is mediated by the CYP2D6 enzyme. It is recommended that strong CYP2D6 inhibitors should be avoided whenever possible in people taking tamoxifen. Examples of such drugs include paroxetine and fluoxetine.[36]

Antidepressants and hyponatraemia

Most antidepressants have been associated with hyponatraemia. However, it has been reported more frequently with SSRIs than with other antidepressants. The onset is usually within 30 days of starting treatment (median 11 days). The most likely mechanism of this adverse effect is the syndrome of inappropriate secretion of antidiuretic hormone.[25,26] Hyponatraemia should be considered in all people who develop dizziness, drowsiness, confusion, nausea, muscle cramps, or seizures. If suspected, stop the antidepressant and manage appropriately.[2,26] Serum sodium should be determined (at baseline and two and four weeks, and then three monthly) for those at high risk of drug-induced hyponatraemia. High-risk factors are as follows:[25]

- Older age.
- Female sex.
- Major surgery.
- History of hyponatraemia or a low baseline sodium concentration.
- Co-therapy with other drugs known to be associated with hyponatraemia (e.g. diuretics, NSAIDs, antipsychotics, carbamazepine, cancer chemotherapy, calcium antagonists, ACE inhibitors and laxatives).
- Reduced renal function (GFR < 50mL/min).
- Medical co-morbidity (e.g. hypothyroidism, diabetes, COPD, hypertension, head injury, CCF, CVA, various cancers).
- Low body weight.

Age is perhaps the most important risk factor, so for older people (especially women) monitoring is essential.[25]

Antidepressants in older people

When prescribing antidepressant medication for older people NICE recommends taking into account the person's general physical health, comorbidities and possible interactions with any other medicines they may be taking. The person should be monitored carefully for side effects and the prescriber should be alert to an increased risk of falls, fractures and hyponatraemia (particularly in those with other risk factors for hyponatraemia, such as concomitant use of diuretics).[1]

Antidepressants and suicidal behaviour

The use of antidepressants has been linked with suicidal thoughts and behaviour; children, young adults, and people with a history of suicidal behaviour are particularly at risk. Where necessary people should be monitored for suicidal behaviour, self-harm, or hostility, particularly at the beginning of treatment or if the dose is changed.[26]

Serotonin syndrome

Serotonin syndrome or serotonin toxicity is a relatively uncommon adverse drug reaction caused by excessive central and peripheral serotonergic activity. Onset of symptoms, which range from mild to life-threatening, can occur within hours or days following the initiation, dose escalation, or overdose of a serotonergic drug, the addition of a new serotonergic drug, or the replacement of one serotonergic drug by another without allowing a long enough washout period in-between, particularly when the first drug is an irreversible MAOI or a drug with a long half-life. Severe toxicity, which is a medical emergency, usually occurs with a combination of serotonergic drugs, one of which is generally an MAOI.[26] Switching to or from an MAOI, or from one MAOI to another, will need to take place in, or with advice from, secondary care.[1]

The characteristic symptoms of serotonin syndrome fall into three main areas, although features from each group may not be seen in all people. Neuromuscular hyperactivity (such as tremor, hyperreflexia, clonus, myoclonus, rigidity), autonomic dysfunction (tachycardia, blood pressure changes, hyperthermia, diaphoresis, shivering, diarrhoea), and altered mental state (agitation, confusion, mania).[26] The most severe cases of serotonin syndrome involve an MAOI (including moclobemide) and an SSRI.[2] Treatment consists of withdrawal of the serotonergic medication and supportive care; specialist advice should be sought.[26]

Anticholinergic burden

An increasing number of systematic reviews and meta-analyses report that medicines with anticholinergic effects are associated with an increased risk of cognitive impairment, falls and all-cause mortality in older people. Combining medicines with anticholinergic activity might have cumulative harmful effects when given to a person with more than one clinical condition. This potential for harm increases with frailty and age. PrescQIPP Bulletin 253: Anticholinergic burden reviews treatment with anticholinergic drugs which includes some antidepressants.[37] The Anticholinergic Cognitive Burden (ACB) Scale lists possible anticholinergics with a score of 1; definite anticholinergics include those listed with a score of 2 or 3.

ACB scores of antidepressants:[38]

- ACB score of 1 – venlafaxine, trazodone and fluvoxamine.
- ACB score of 2 – none.
- ACB score of 3 – amitriptyline, clomipramine, doxepin, imipramine, nortriptyline, paroxetine and trimipramine.

Antidepressants in breastfeeding

Untreated or inadequately treated depression can have adverse effects on the mother and infant and it is important that the mother receives effective treatment and does not stop taking an antidepressant suddenly. Treatment choice should primarily focus on controlling the mother's symptoms. Safety in breastfeeding is a secondary consideration. Paroxetine and sertraline are the SSRIs of choice during breastfeeding due to low levels in breast milk and favourable drug properties. However there is no need to change an SSRI used successfully during pregnancy to a preferred choice in breastfeeding as long as the infant has been born full term and healthy.[39]

More evidence is available on the use of SSRIs during breastfeeding than other antidepressant groups and limited data show encouraging outcomes when considering longer term effects on infants. However, they all have relatively long half-lives. This could result in accumulation and increased risk of side-effects due to an infant's underdeveloped clearance capacities, particularly in the neonatal period. Paroxetine and sertraline have shorter half-lives and pass into milk in smaller amounts compared to others and are therefore preferred.[39]

SSRIs can cause discontinuation symptoms if stopped abruptly and occurs most commonly with paroxetine. This may make it more difficult for a breastfeeding mother to stop treatment and should be considered when making medicine choices.[39]

Neonatal withdrawal syndrome has been reported in infants exposed to SSRIs later in pregnancy, most commonly with paroxetine. Symptoms include poor adaptation, jitteriness, irritability, poor gaze, agitation, hypotonia, and gastro-intestinal disturbances. Symptoms typically last one to two days (potentially longer with fluoxetine) but should resolve without intervention. Continuing breastfeeding may relieve withdrawal effects. It may be difficult to distinguish between neonatal withdrawal symptoms and potential side-effects from SSRI exposure through breast milk. Symptoms common to both include agitation, jitteriness, hypotonia, and gastro-intestinal disturbances. Sedation has only been reported after exposure through breast milk. If symptoms do not resolve a few days after birth, consider that side-effects may be the potential cause.[39]

Those taking an SSRI may have more difficulty breastfeeding, particularly with establishing breastfeeding. The underlying disease state may contribute to this and additional breastfeeding support may be required.[39]

NICE clinical guidance Antenatal and postnatal mental health: clinical management and service guidance [CG192] recommends considering a TCA, SSRI or SNRI for more severe depression in pregnancy or the postnatal period if the woman understands the risks associated with the medication and the mental health problem in pregnancy and the postnatal period and:

- She has expressed a preference for medication, or;
- She declines psychological interventions, or;
- Her symptoms have not responded to psychological interventions.[16]

Co-morbid conditions

A chronic physical health problem can both cause and exacerbate depression. Pain, functional impairment and disability associated with chronic physical health problems can greatly increase the risk of depression in people with physical illness. Depression can also exacerbate the pain and distress associated with physical illnesses and adversely affect outcomes, including shortening life expectancy. Depression can be a risk factor in the development of a range of physical illnesses, such as cardiovascular disease. When a person has both depression and a chronic physical health problem, functional impairment is likely to be greater than if a person has depression or the physical health problem alone. Depression is approximately two to three times more common in people with a chronic physical health problem than in people who have good physical health and occurs in about 20% of people with a chronic physical health problem.[7]

NICE clinical guidelines [CG91] Depression in adults with a chronic physical health problem: recognition and management does not recommend using antidepressants routinely to treat subthreshold depressive symptoms or mild depression in people with a chronic physical health problem (because the risk–benefit ratio is poor), but consider them for people with any of the following:[7]

- A past history of moderate or severe depression.
- Mild depression that complicates the care of the physical health problem.
- Initial presentation of subthreshold depressive symptoms that have been present for a long period (typically at least two years).
- Subthreshold depressive symptoms or mild depression that persist(s) after other interventions.

When an antidepressant is to be prescribed for a person with depression and a chronic physical health problem, (such as cancer, heart disease, diabetes, or a musculoskeletal, respiratory or neurological disorder) take into account the following:[7]

- The presence of additional physical health disorders.
- The side effects of antidepressants, which may impact on the underlying physical disease (e.g. 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 people with particular chronic physical health problems.
- Interactions with other medications.

Coronary heart disease (CHD)

Depression is common in people with CHD. It is associated with higher risk of death due to cardiovascular causes and so it is important that it is well-managed. Making a suitable choice needs to include consideration of both the characteristics of the medicines available and those of the

person. Prescribers may need to choose a safe antidepressant in people with CHD. These preferred antidepressants have data to demonstrate safe use in people with CHD and have minimal or no effects on the cardiovascular system:[40]

- SSRIs are the preferred antidepressants in CHD.
- Sertraline, fluoxetine, or paroxetine are the SSRIs of choice.
- Mirtazapine is also a preferred antidepressant in CHD.

Consider gastroprotection as SSRIs increase the risk of gastrointestinal bleeding, particularly in older people and in those who take aspirin and SSRIs.[7,40]

Preferred antidepressants should be used first-line, but there may be a good reason why they cannot. The options below are preferred less as there is less data to demonstrate safe use in people with CHD and/or they have demonstrated effects on the cardiovascular system:[40]

- Citalopram and escitalopram should generally be avoided. In particular do not use citalopram in people with known QT interval prolongation, congenital long QT syndrome or in people taking other medicines that prolong the QT interval.
- If citalopram and escitalopram are the only feasible antidepressant options:
  - The MHRA advises that both citalopram and escitalopram be subject to additional monitoring in patients with CHD.[31]
  - Use citalopram with extreme caution in people with CHD, particularly in those with recent MI, bradyarrhythmias/bradycardia, hypokalaemia or hypomagnesaemia or decompensated heart failure.
- TCAs should generally be avoided. Doxepin, lofepramine and mianserin may be considered lower risk, but should still be used with caution. If TCAs are the only feasible option, consider ECG monitoring (at baseline and a week after dose increases), particularly in those who may be vulnerable to arrhythmias.
- MAOIs should almost always be avoided. Where they are used, they will usually be initiated by mental health specialists after careful consideration. Of the MAOIs moclobemide is considered a lower risk option.
- Agomelatine and vortioxetine may be considered third line options.
- Duloxetine, reboxetine, and venlafaxine should be avoided if possible.

Diabetes

There is an established link between diabetes and depression. Having diabetes doubles the odds of co-morbid depression, and a diagnosis of diabetes is linked to an increased likelihood of an antidepressant prescription. People with depression and diabetes have a high number of cardiovascular risk factors and a 50% increased risk of mortality. Studies indicate that SSRIs have a favourable effect on diabetic parameters in people with type II diabetes and should be used first-line, there is data supporting sertraline, escitalopram and fluoxetine. SNRIs and agomelatine are also likely to be safe, but there is less supporting data. TCAs and MAOIs should be avoided if possible due to their effects on weight and glucose homeostasis. Blood glucose and HbA1c should be monitored carefully when antidepressant treatment is initiated, when the dose is changed and after discontinuation.[25]

Epilepsy

Antidepressants are not contra-indicated in stable epilepsy; however, they should be prescribed with caution in people with epilepsy or a history of seizures.[2,41] The relatively low risk of antidepressants affecting seizure threshold rarely outweigh the risk of leaving depression untreated.[41] The Maudsley Guidelines recommend SSRIs (citalopram/escitalopram followed by sertraline) and mirtazapine as low

risk in people with epilepsy. SSRIs may be anticonvulsant at therapeutic doses and proconvulsant in overdose.[25] The NICE guidance on depression recommends SSRIs, such as sertraline or citalopram, as being suitable for people with chronic health problems.[7,41] Preferred options of low to moderate risk antidepressants in no order of preference include:[41]

- Citalopram.
- Escitalopram.
- Fluoxetine.
- Sertraline.

Switching antidepressant medication

NICE recommends increasing antidepressant dose or changing the drug if a person's depression has had no or a limited response to treatment with antidepressant medication and no obvious cause can be found and resolved. For example, by:[1]

- Switching to another medication in the same class (for example, another SSRI).
- Switching to a medication of a different class (for example, an SSRI, SNRI, or in secondary care a TCA or MAOI). Take into account that:
  - Switching medication may mean cross-tapering is needed.[1]
  - Switching to or from an MAOI, or from one MAOI to another, will need to take place in, or with advice from, secondary care.[1]
  - Take into account that switching medication may mean that an adequate wash-out period is needed, particularly when switching to or from irreversible MAOIs or moclobemide.[1]
  - TCAs are dangerous in overdose, although lofepramine has the best safety profile.[1]
  - Prescribers in primary care should not initiate dosulepin and should deprescribe in all people where appropriate - PrescQIPP Bulletin 310: Dosulepin.[27]
  - Prescribers in primary care should not initiate trimipramine and should deprescribe in all people where appropriate - PrescQIPP Bulletin 311: Trimipramine.[27]
- Consider whether some of these decisions and treatments need other services to be involved (for example, specialist mental health services for advice on switching antidepressants).[1]

In cases of non-response, there is some evidence that switching within a drug class is effective, but switching between classes is, in practice, the most common option and is supported by some analyses. Switching between drug classes in cases of poor tolerability is supported by some studies and has a strong theoretical basis. In practice, many people who cannot tolerate one SSRI will readily tolerate another.[25]

In general, when changing from one antidepressant to another, abrupt withdrawal should be avoided unless there has been a serious adverse event. Cross-tapering is preferred, in which the dose of the ineffective or poorly tolerated drug is slowly reduced while the new drug is slowly introduced. The speed of cross-tapering is best judged by monitoring tolerability. Few studies have been done, so caution is required. Extended periods may be necessary to mitigate withdrawal symptoms.[25]

Table 6: Example cross-tapering[25]

Example	Week 1	Week 2	Week 3	Week 4
Withdrawing citalopram 40mg daily	20mg daily	10mg daily	5mg daily	2.5mg daily
Introducing mirtazapine	15mg at night	30mg at night	30mg at night	45mg at night (if increase is required)

In some cases, cross-tapering may not be necessary. An example is when switching from one SSRI to another, their effects are so similar that administration of the second drug is likely to ameliorate withdrawal effects of the first. The use of fluoxetine has been advocated as an abrupt switch treatment for SSRI discontinuation symptoms. Abrupt cessation may also be acceptable when switching to a drug with a similar, but not identical, mode of action. In some cases, abruptly stopping one antidepressant and starting another antidepressant at the usual dose may not only be well tolerated but may also reduce the risk and severity of discontinuation symptoms.[25]

Potential dangers of simultaneously administering two antidepressants include pharmacodynamic interactions (serotonin syndrome, hypotension, drowsiness; depending on the drugs involved) and pharmacokinetic interactions (e.g. elevation of tricyclic plasma levels by some SSRIs). Serotonin syndrome can occur with a single serotonergic drug at a therapeutic dose or more frequently in combination of serotonergic drugs or in overdose. Most severe cases of serotonin syndrome involve an MAOI (including moclobemide) plus an SSRI. Caution is advised when switching strategies call for the combining of serotonergic drugs. Serotonin syndrome symptoms include:[25]

- Mild – Insomnia, anxiety, nausea, diarrhoea, hypertension, tachycardia, hyper-reflexia.
- Moderate – Agitation, myoclonus, tremor, mydriasis, flushing, diaphoresis, low fever (<38.5˚C).
- Severe – Severe hyperthermia, confusion, rigidity, respiratory failure, coma, death.

NICE Clinical Knowledge Summary on switching antidepressants has information on switching to another antidepressant:[42]

- From an SSRI (not fluoxetine).
- From fluoxetine.
- From trazodone.
- From an SNRI.
- From a TCA.
- From mirtazapine.
- From reboxetine.

The Specialist Pharmacy Service also have advice on antidepressant switching with guides on establishing if a person needs to switch their antidepressant, choosing an antidepressant to switch to, agreeing a strategy, and monitoring. They also give advice on suitable strategies for a range of potential switches:[43]

- SSRIs to other antidepressants: switching in adults
- Mirtazapine to other antidepressants: switching in adults
- SNRIs to other antidepressants: switching in adults
- Tricyclics to other antidepressants: switching in adults
- MAOI to other antidepressants: switching in adults
- Moclobemide to other antidepressants: switching in adults
- Trazodone to other antidepressants: switching in adults
- Vortioxetine to other antidepressants: switching in adults
- Agomelatine to other antidepressants: switching in adults

The Maudsley Prescribing Guidelines provide detailed advice on switching between classes of antidepressants which should be treated with caution and people should be very carefully monitored when switching.[25] It is recommended to refer to local prescribing guidelines and/or specialist psychiatric advice when swapping antidepressant medication. The specific SPCs for each of the antidepressants involved should be consulted. There are no clear guidelines on switching antidepressants, so caution is required.[44]

Stopping antidepressants

When prescribing antidepressant medication ensure people are advised that:[1]

- Treatment might need to be taken for at least six months after the remission of symptoms but should be reviewed regularly.
- They should talk with the person who prescribed their medication (for example, their primary healthcare or mental health professional) if they want to stop taking it. It should be explained that it is usually necessary to reduce the dose in stages over time (called 'tapering').
- If they stop taking it abruptly, miss doses or do not take a full dose, they may have withdrawal symptoms.
- Withdrawal symptoms do not affect everyone and can vary in type and severity between individuals. Symptoms may include:
  - Unsteadiness, vertigo or dizziness
  - Altered sensations (for example, electric shock sensations)
  - Altered feelings (for example, irritability, anxiety, low mood tearfulness, panic attacks, irrational fears, confusion, or very rarely suicidal thoughts)
  - Restlessness or agitation
  - Problems sleeping
  - Sweating
  - Abdominal symptoms (for example, nausea)
  - Palpitations, tiredness, headaches, and aches in joints and muscles.
- Withdrawal symptoms can be mild, may appear within a few days of reducing or stopping antidepressant medication, and usually go away within one to two weeks.
- Withdrawal can sometimes be more difficult, with symptoms lasting longer (in some cases several weeks, and occasionally several months).
- Withdrawal symptoms can sometimes be severe, particularly if the antidepressant medication is stopped suddenly.
- Some commonly used antidepressants such as paroxetine and venlafaxine, are more likely to be associated with withdrawal symptoms, so particular care is needed with them.

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 stepwise 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. People should be monitored and reviewed whilst their dose is reduced for withdrawal symptoms and the return of depression symptoms. The frequency of monitoring should be based on the person's clinical and support needs.[1] It is difficult to predict the exact period required for an individual to taper off antidepressant medication, but most long-standing treatments take around three months and some up to two years. Below is a guide to tapering sertraline according to an exponential pattern. The reductions are equivalent to about 10–20% dose reductions at each step:[25]

- Reduce dose by 12.5–25mg every two to four weeks until reaching 50mg per day.
- Reduce by 2–5mg every two to four weeks until reaching 15mg per day, then;
- Reduce by 1–2mg every two to four weeks until reaching 9mg per day, then;
- Reduce by 0.4–1mg every two to four weeks until reaching 4mg per day, then;
- Reduce by 0.2–0.4mg every two to four weeks until reaching 2mg per day, then;
- Reduce by 0.1–0.25mg every two to four weeks until completely stopped.

Withdrawal symptoms can be experienced with a wide range of antidepressant medication including TCAs, SSRIs, SNRIs, and MAOIs. Some commonly used antidepressants such as paroxetine and venlafaxine, are more likely to be associated with withdrawal symptoms, so particular care is needed with them. Fluoxetine's prolonged duration of action means that it can sometimes be safely stopped in the following way:[1]

- In people taking 20mg fluoxetine a day, a period of alternate day dosing can provide a suitable dose reduction.
- In people taking higher doses (40mg to 60mg fluoxetine a day), use a gradual withdrawal schedule.
- Allow one to two weeks to evaluate the effects of dose reduction before considering further dose reductions.

If withdrawal symptoms become intolerable at any point, either hold the current dose for longer to allow them to resolve, or if very unpleasant, increase to the last dose at which the symptoms were tolerable, and remain there until symptoms resolve. After stabilisation, tapering will need to be more gradual, with reduction in smaller amounts and/or longer periods in between reductions. Some people find that they cannot reduce at more than 5% of the last dose a month. If a person experiences distressing withdrawal symptoms, it does not indicate that they cannot stop antidepressants, but that they will need to taper more slowly, with smaller reductions than they have been undertaking.[25]

The webinar and questions and answer session Developing pragmatic, evidence based strategies to help people safely and calmly taper off and stop antidepressant therapy led by Dr Mike Scanlan is aimed to equip participants with a range of applicable and common sense approaches and tools that can help patients to manage anxiety, cope with physical discomfort, and maintain psychological wellbeing whilst coming off medication. The session teaches participants a range of thought defusion skills, willingness and acceptance mindful approaches and positive psychology approaches aimed at supporting and enhancing wellbeing.

Cost

£276.9 million is spent annually on the prescribing of antidepressant medication in England, Wales, Isle of Man and Scotland NHSBSA (May 22 to April 23), Public Health Scotland (April 22 to March 23). In England, Wales and Isle of Man there was a 3.14% growth in antidepressant items and 0.45% growth in antidepressant costs between May 22 to April 23 compared to May 21 to April 22. In Scotland, there was a 2.01% growth in antidepressant items between April 22 to March 23 compared to April 21 to March 22.

For each antidepressant, the World Health Organisation (WHO) have Defined Daily Doses (DDD).[45] Table 7 shows the 28-day costs based on the WHO DDD for each antidepressant. Drugs are listed in increasing order of cost based on their WHO DDDs.

Table 7: Antidepressant cost based on WHO DDD.[45,46] Please note, doses in the following table are NOT equivalent

Antidepressant	Class	WHO DDD (mg)	Formulation	Cost for 28 days based on WHO DDD
Mirtazapine	Noradrenaline and specific Serotonin antidepressant (NaSSa)	30mg	Mirtazapine 30mg tablets x 28	£0.99
Sertraline	SSRI	50mg	Sertraline 50mg tablets x 28	£1.04
Fluoxetine	SSRI	20mg	Fluoxetine 20mg capsules x 28	£1.16

Antidepressant	Class	WHO DDD (mg)	Formulation	Cost for 28 days based on WHO DDD
Escitalopram	SSRI	10mg	Escitalopram 10mg tablets x 28	£1.28
Citalopram	SSRI	20mg	Citalopram 20mg tablets x 28	£1.36
Paroxetine	SSRI	20mg	Paroxetine 20mg tablets x 28	£1.51
Nortriptyline	TCA	75mg	Nortriptyline 25mg tablets x 84	£1.81
Amitriptyline	TCA	75mg	Amitriptyline 25mg tablets x 84	£2.25
Duloxetine	SNRI	60mg	Duloxetine 60mg gastro-resistant capsules x 28	£2.68
Venlafaxine	SNRI	100mg	Venlafaxine 150mg modified release tablets x 28	£3.64
Trazodone	TCA	300mg	Trazodone 150mg tablets x 56	£4.64
Venlafaxine	SNRI	100mg	Venlafaxine 150mg modified release capsules x 28	£4.72
Venlafaxine	SNRI	100mg	Venlafaxine 37.5mg tablets x 84	£5.61
Imipramine	TCA	100mg	Imipramine 25mg tablets x 112	£5.68
Lofepramine	TCA	105mg	Lofepramine 70mg tablets x 56	£12.11
Moclobemide	MAOI	300mg	Moclobemide 300mg tablets x 28	£13.06
Agomelatine	Melatonin receptor agonist	25mg	Agomelatine 25mg tablets x 28	£15.25
Clomipramine	TCA	100mg	Clomipramine 50mg capsules x 56	£16.18
Dosulepin	TCA	150mg	Dosulepin 75mg tablets x 56	£16.86
Fluvoxamine	SSRI	100mg	Fluvoxamine 100mg tablets x 28	£17.10
Reboxetine	Selective inhibitor of noradrenaline reuptake (NaRI)	8mg	Reboxetine 4mg tablets x 56	£17.65
Vortioxetine	Serotonin modulator and stimulator (SMS)	10mg	Vortioxetine 10mg tablets x 28	£27.72
Mianserin	Tetracyclic antidepressant (TeCA)	60mg	Mianserin 30mg tablets x 56	£96.88

Antidepressant	Class	WHO DDD (mg)	Formulation	Cost for 28 days based on WHO DDD
Doxepin	TCA	100mg	Doxepin 50mg capsules x 56	£308.00
Tranylcypromine	MAOI	10mg	Tranylcypromine 10mg tablets x 28	£514.49
Trimipramine	TCA	150mg	Trimipramine 50mg capsules x 84	£652.50

Sertraline, escitalopram and mirtazapine compared with other antidepressants are less costly and have higher response and lower dropout rates.[25,46] They should be considered for formulary inclusion and as first choices in new diagnosis where suitable for the individual.

Table 8: Antidepressant liquid formulations cost based on WHO DDD.[45,46]

Antidepressant	Class	WHO DDD (mg)	Formulation	Cost for 28 days based on WHO DDD
Mirtazapine	Noradrenaline and specific Serotonin antidepressant (NaSSa)	30mg	Mirtazapine 30mg orodispersible tablets x 28	£1.73
Fluoxetine	SSRI	20mg	Fluoxetine 20mg dispersible tablets sugar free x 28	£3.44
Citalopram	SSRI	20mg	Citalopram 40mg/ml oral drops sugar free* x 14ml	£11.06
Sertraline	SSRI	50mg	Sertraline 50mg/5ml oral suspension **(UNLICENSED SPECIAL)** x 140ml	£14.86
Escitalopram	SSRI	10mg	Escitalopram 20mg/ml oral drops sugar free x 14ml	£18.82
Fluoxetine	SSRI	20mg	Fluoxetine 20mg/5ml oral solution x 140ml	£25.54
Fluoxetine	SSRI	20mg	Fluoxetine 20mg/5ml oral solution sugar free x 140ml	£25.90

*Citalopram drops are not bioequivalent to citalopram tablets - 4 oral drops (8 mg) are equivalent in therapeutic effect to one 10 mg tablet.[26]

The most cost-effective liquid preparation for people who have swallowing difficulties based on the WHO DDD is mirtazapine 30mg orodispersible tablets. The most cost-effective SSRI available in liquid form is fluoxetine 20mg dispersible tablets. Fluoxetine 20mg dispersible tablets are less costly than both fluoxetine oral solution and sugar free oral solution.[46] The 20mg dispersible fluoxetine tablet is also scored so it can be divided into equal halves to reduce or increase to dose as needed.[47]

Savings

Based on prescribing data from NHSBSA (May 22 to April 23) and Public Health Scotland (April 22 to March 23) for England, Wales, Scotland and Isle of Man.

- Reviewing patients on long term antidepressants and stopping (after tapering) the antidepressant in 10% of patients could **save £18 million annually or £25,207 per 100,000 population**.
- Using the cost-effective antidepressants (sertraline, escitalopram and mirtazapine) instead of dosulepin, trimipramine, clomipramine, fluvoxamine, reboxetine, and trazodone, **could provide savings of £11.8 million annually or £16,538 per 100,000 population.**
- Using fluoxetine 20mg dispersible tablets instead of fluoxetine oral solution and sugar free oral solution could **save £3 million annually or £4,207 per 100,000 population**.

Summary

Antidepressant medication should not be routinely offered as first-line treatment for less severe depression, unless that is the person's preference. SSRIs are recommended as a treatment option for people with less severe depression.[1]

Treatment options for a new episode of more severe depression include a combination of individual CBT and an antidepressant. Antidepressant medication for more severe depression can be a SSRI, SNRI, or other antidepressant if indicated based on previous clinical and treatment history. SSRIs are generally well tolerated, have a good safety profile and should be considered as the first choice for most people.[1]

There is little to choose between the different classes of antidepressant drugs in terms of efficacy, so choice should be based on the individual person's requirements, including the presence of concomitant disease, existing therapy, suicide risk, and previous response to antidepressant therapy.[26] In the absence of special factors, antidepressants that are better tolerated and safer in overdose should be chosen. There is most evidence for SSRIs which, together with other newer antidepressants, are first line choices.[23]

Sertraline, escitalopram and mirtazapine compared with other antidepressants are less costly and have a higher response and lower dropout rates.[28,46] They should be considered for medicines formulary inclusion and as first choices in new diagnosis where suitable for the individual.

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Additional PrescQIPP resources

Briefing	https://www.prescqipp.info/our-resources/bulletins/bulletin-330-antidepressants
Implementation tools	

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