NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINE

Depression treatment, for adults, in primary care

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

Contents

Integrated Care Pathway (Appendix 1)

Holistic Assessment

- Symptoms present for 2 weeks or more (as per ICD-11 classification).
- Patient centred physical, social and psychological assessment.
- Consider: PHQ-9 (see accompanying notes), CORE 10 or other suitable assessment tool.
- Consider: alcohol (FAST tool), substance misuse, significant life events (e.g. bereavement, etc) exclude organic disease (e.g. hypothyroidism, anaemias, etc).
- **Assess risk of self-harm, suicide and risk to others**.

Consider Bipolar Disorder: Assessment and Management - NICE 185. Please consider:

- Past history of manic symptoms: over activity; decreased need for sleep; euphoria/elation; inflated self-esteem/grandiosity; pressured speech/racing thoughts, distractibility, social disinhibition, excessive spending.
- Strong family history of bipolar disorder or psychosis.
- Referral: Community Mental Health Team (CMHT).
- Antidepressant monotherapy is not recommended for bipolar illness.

Consider Anxiety Disorders – NICE 113

Diagnosis Depression[1]

- Read Code depressive episode.
- If severe depression (including psychotic symptoms) or suicide risk, consider CMHT referral or out of hours review at CMHT hub; referral either by practitioner or patient by contacting 0845 650 1730.
- Depressive symptoms in adolescents refer for specialist assessment.

Treatment

- **Mild:** Self-help, stress and wellbeing education, psychoeducation groups and classes, Computerised CBT (via SCI gateway), Websites: Wellbeing, Lifelink. Watch, Wait and Review.
- **Recurrence:** Start previous effective antidepressant (increasing to previously effective dose) & self help.
- **Moderate/Severe:** Antidepressant & self-help +/- referral (psychological therapy or further assessment).

Frequency of review will vary with individuals needs, for example every 2–4 weeks (or more frequently if self-harm or suicide risk) within the first 3 months and then at longer intervals if good response.

For the first episode of depression the majority of patients will remit within 6 to 12 months.

Low mood due to adjustment and reactive effects; social factors and life events associated with symptoms, consider: Lifelink; Citizens Advice; Wellbeing

Self-help and Non-pharmacological Therapy

Consider a range of approaches for all forms of depression

- **Life-style:** Structured day, exercise, alcohol and/or drug use, diet, sleep hygiene; caffeine intake, etc.
- **Exercise:** Structured exercise programme: Live Active.
- **Self-help:** Information websites & telephone numbers (Appendix 2)
  - Health reading section in libraries.
  - Computerised Cognitive Behavioural Therapy (CBT), refer via SCI gateway.
  - Websites Wellbeing information and downloadable resources. Other useful sites: Living Life to the Full and apps Headspace
- **Support** patients to problem solve: Information websites & telephone numbers (Appendix 2).
- **Primary Care Mental Health Team (PCMHT):** consider referral if: symptoms meet diagnostic criteria, individual is motivated and able to engage in structured psychological therapy e.g. CBT

Review Regularly to Support Patients and Improve Outcomes

Self-help and Non-pharmacological Therapy plus Antidepressant

- Spontaneous remission: about 50% of patients recover from first episode within 3 months.[2]
- All antidepressants are equally efficacious when treatment doses are taken regularly.
- Consider: co-morbidities, pregnancy, breast-feeding, interacting medicines, etc.
- Consider: limit antidepressant supply where risk of suicide.
- There is a slight increased risk of suicide when initiating antidepressants (see below).

Information which may be of use to patients, carers and family

- Have realistic expectations. You will still have bad days and setbacks.
- Antidepressants are not addictive. But may cause withdrawal/discontinuation symptoms for some.
- Any thoughts of self-harm please contact your practice, out of hours service (NHS 24, Tel: 111), friend or a family member.
- You may feel benefit when first starting an antidepressant but it can take 2 to 4 weeks to provide its full effect.
- If symptoms are not improving the antidepressant or antidepressant dose might have to be changed.
- You should take your antidepressant for at least 6 months after you feel better. If you have had 2 or more episodes in the recent past the antidepressant may be continued for up to 2 years.
- Side effects can be short lived; reducing within a few weeks of starting an antidepressant.
  - SSRIs: nausea, vomiting, diarrhoea, anxiety, weight loss/gain, headache, insomnia
    Agitation is a common side effect associated with starting and increasing SSRIs doses which normally resolves within 7-10 days, but can contribute to suicidal ideation. If this occurs please contact your practice.
  - TCAs: dry mouth, constipation, drowsiness, dizziness, increased appetite, weight gain, confusion.
  - Mirtazapine: sedation (especially at lower doses: 15mg daily), increased appetite, weight gain.
  - Trazodone: sedation, headache, nausea, vomiting, hypotension, priapism.
  - Venlafaxine: constipation, nausea, vomiting, weight loss, palpitations, hypertension.

  If side effects continue or are troublesome please discuss alternative treatment options with your GP.
- Discontinuation symptoms may occur on stopping, missing doses or when reducing the dose; these are usually mild and self-limiting but can be severe when antidepressants are stopped abruptly.
- More medicines information available at NHS Choices Antidepressants and Choice and Medication
- Avoid alcohol and recreational drugs.
- Self-help: Information websites & telephone numbers (Appendix 2). Healthy reading section in local libraries. For the first episode of depression the majority of patients will remit within 6 to 12 months.
- Have realistic expectations. You will still have bad days and setbacks.

Check – Do they want to take an antidepressant?
Discuss starting and stopping treatment

Mild depression
Watch, Wait & Review

Antidepressants demonstrate poor benefit.

Non-pharmacological therapy and self-help: sign-posting, psychoeducation.

Recurrence
Mild, moderate or severe

Start previous effective antidepressant. Increase to previously effective dose. Discuss withdrawal risk.

Plus non-pharmacological therapy and self-help.

Moderate/Severe depression
Sertraline or fluoxetine or citalopram or mirtazapine

Trial therapeutic dose: 50mg sertraline, 20mg fluoxetine/citalopram or mirtazapine 30mg daily. Discuss withdrawal risk. Assess efficacy at 2-4 weeks.

SSRIs demonstrate a flat dose response curve for the treatment of depression[4-6] Plus non-pharmacological therapy & self-help.

Review Regularly to Support Patients and Improve Outcomes

Review physical, social and psychological assessment, progress (PHQ-9, CORE-10) and treatment efficacy.

Watch & Wait: Assess response and severity. A large proportion of patients will spontaneously remit.
No response at 4 weeks with therapeutic dose taken regularly.

- Check concordance. Review diagnosis: exclude organic cause, bipolar illness, etc.
- A lack of significant improvement in concordant patients after 2-4 weeks of treatment reduces the probability of an eventual response.[4,7]
- Consider increasing to therapeutic daily dose: ***'50's enough'*** for sertraline, ***'20's plenty'*** for fluoxetine/citalopram, or 30mg of mirtazapine where night-time sedation is required. Higher doses increases the risk of avoidable adverse drug effects with little clinical benefit.[4-6]
- Consider switch to alternative Formulary antidepressant. Lofepramine increasing to 140mg daily may also be an appropriate formulary option.
- Consider referring to PCMHT, if symptoms meet diagnostic criteria, individual is motivated and able to engage in structured psychological therapy e.g. CBT, and antidepressant and dose are stable.

Partial response at 4 weeks with therapeutic dose taken regularly.

- Check concordance.
- Consider switching antidepressant or increasing current antidepressant dose (evidence is lacking to support increasing SSRI doses[3-6]) and review efficacy 2-4 weeks.
- If residual symptoms persist after increasing the dose, consider switch to an alternative antidepressant, see NHSGGC Formulary.
- Consider referring to PCMHT as outlined above.

Do NOT combine antidepressants unless directed by consultant psychiatrist.

Full response: Maintain current antidepressant and dose after remission achieved.

- First episode: continue for **6 months** after remission achieved; reviewing according to need.
- Recurrent episodes: consider number of relapses and tailor treatment to patients needs with regular review: at least **1 year** of treatment after full remission for those at increased risk and at least **2 years** in higher risk patients (i.e. >5 lifetime episodes and/or 2 episodes in the last few years[3,8]).
- Long-term use: review regularly every 6-12 months; consider adding review date to prescription.
- **Review ongoing need.** Consider reducing and stopping after patient has completed the course.

Third line choices: **venlafaxine** is restricted to use as third line agent for depression. The MR preparation is restricted to initiation on the advice of a consultant only, as MR/XL preparations lack clear clinical advantages over standard release. Increase to 225mg if appropriate, and tolerated, for dual effect. Regularly monitor BP as clinically appropriate.

Duloxetine restricted to psychiatrist initiation as third line therapy for major depressive episodes.

Avoid St John's wort (Hypericum). Due to drug-interactions and lack of standardised dose.

Depression with anxiety

- Consider relaxation resources Wellbeing.
- Consider referral to PCMHT, if co-morbid anxiety disorder.
- Agitation is a common side effect associated with starting and increasing SSRIs doses which normally resolves within 10 days, but can contribute to suicidal ideation.
- If a patient is very anxious or agitated, consider the use of benzodiazepines as an adjunct for a maximum of 2 weeks. Use lowest possible dose.
- Avoid long-term (>4 weeks) benzodiazepines or z-hypnotics as they can increase anxiety and worsen depressive symptoms.

Antidepressant switching, stopping, dose and preparation information:

- **Switching antidepressants:** Consider patient's age, frailty, co-morbidities, other medicines, the antidepressant's half-life, pharmacodynamics and interaction risks with other medicines/co-morbidities. Cross tapering is preferred. However, some switches require a washout period e.g. from fluoxetine due to long half-life. Simultaneously administering two antidepressants increases the risk of interactions: pharmacodynamic (serotonin syndrome, drowsiness, etc) and pharmacokinetic (raised tricyclic antidepressant (TCA) levels with some SSRIs), see Clinical Knowledge Summaries (CKS) Switching. When switching, including within class, response rates vary widely from 12–70% in different studies.[3]

	Current	Week 1	Week 2	Week 3
Citalopram	40mg daily	20mg daily	10mg daily	Stop
Mirtazapine	Nil	15mg/d	30mg daily	30mg daily

	Current	Week 1	Week 2
Citalopram	40mg daily	20mg daily	stop
Sertraline	Nil	Nil	Sertraline 50mg daily

Note tables are provided as examples. Clinicians should consider patient and medicines related factors e.g. lower reduction and starting doses with older adults.

- **Stopping**: All classes of antidepressants can cause discontinuation/withdrawal symptoms, when abruptly stopped or after missing or reducing doses. Encourage patients to discuss stopping before doing so. Discontinuation symptoms more commonly occur with higher doses and longer duration of treatment. Symptoms begin within a few days of stopping and generally subside within 7-10 days, but some patients may experience severe or prolonged symptoms (flu-like, electric shocks, vivid dreams, insomnia, etc). The optimum rate of taper to prevent withdrawals is unknown. Withdrawal reactions may be mistaken for relapse. Slow reduction over ≥4 weeks, or months may be needed. Speed of reduction should be guided by the patient's wishes and needs – Reducing and stopping advice (Appendix 3).
- **Dose response**: Evidence is lacking for better SSRI and mirtazapine efficacy with higher daily doses: '20's plenty', citalopram/fluoxetine/paroxetine, '50's enough' for sertraline and 30mg of mirtazapine.4-6 Higher TCA and venlafaxine doses can be more effective. 4-6
- **Fluoxetine preparations:** Fluoxetine 20mg capsules are the preferred NHSGGC preparation; 10mg capsules should not be prescribed routinely due to high costs. If 10mg daily doses are needed, 20mg dispersible tablets can be halved or alternate day dosing with 20mg capsules can be used.
- **Venlafaxine preparations:** Are restricted to use as third line agent for depression. Modified release (MR and XL) preparations are restricted to initiation on the advice of a consultant only, as they lack clear clinical advantages over standard release.

Co-morbidity and special groups:

- **Cardiovascular disease:**
  - Arrhythmias: Avoid TCAs. Citalopram is contraindicated in people with known QT prolongation or in combination with drugs known to prolong QT: QT prolongation information. Venlafaxine is contraindicated in people with an identified high risk of serious cardiac ventricular arrhythmia
  - Hypertension: venlafaxine and duloxetine are contraindicated for people with uncontrolled hypertension. For people who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered.
  - Left ventricular systolic dysfunction (LVSD): avoid TCAs, venlafaxine, trazodone. Sertraline or mirtazapine likely to be safer.[7]
  - Post MI or unstable angina: Sertraline preferred with mirtazapine or other SSRIs likely to be safe.[7]

- **Anticoagulants:** Warfarin: monitor INR when antidepressants are initiated, doses changed and after discontinuing. SSRIs: Increased bleeding risk with all anticoagulants, due to SSRI antiplatelet effects.
- **Dementia:** Apathy in dementia is common, and should be differentiated from depression. Antidepressants have moderate effects;[3] for those with depression and dementia. Patients should be routinely reviewed to assess ongoing need**.**
- **Diabetes:** SSRI first line choice.[3,9] Mirtazapine may be considered as an alternative but is associated with weight gain. Avoid TCAs and MAOIs. Monitor blood glucose carefully when antidepressants are initiated, doses are changed and after discontinuation.
- **Elderly:** May require lower starting dose increasing to therapeutic dose. Avoid TCAs where possible due to anticholinergic, cardiovascular and sedative effects.
- **Epilepsy:** Sertraline or mirtazapine may be appropriate for less complex cases. However seek specialist advice. Medicines Information Tel:0141 211 6478 medinfo@ggc.scot.nhs.uk
- **Mental health:** Consider cardiometabolic (lipids, HbA1c, BP, weight/BMI) and renal monitoring for individual's receiving antidepressants in combination with other psychotropic medicines – see NHSGGC Primary Care psychotropic good practice guidance. This group of Individuals are at higher risk of avoidable early death (15-20 years premature) due to metal illness, social and medicines related cardiometabolic effects. Where appropriate consider **'don't just screen, but intervene':** primary prevention, cardiac and diabetes treatment in line with local and national guidelines.
  - Bipolar illness: Lithium and/or antipsychotic cardiometabolic monitoring
  - Psychotic illness: Antipsychotic cardiometabolic monitoring.
  - Treatment resistant depression: Lithium and/or antipsychotic cardiometabolic monitoring.
- **Post stroke:** consider fluoxetine or citalopram or mirtazapine in ischaemic stroke; avoid SSRIs in haemorrhagic stroke due to increased bleeding risk.[8]
- **Pregnant or breast feeding:** Seek specialist advice for individual cases: Perinatal Mental Health Service: 0141 211 6500. Background information available at CKS – Antenatal and Postnatal. Management of perinatal mood disorders – SIGN 127.

Antidepressant Adverse Effects:

Some effects mimic signs and symptoms of depression e.g. SSRIs: insomnia, hypersomnia or anxiety; venlafaxine: anxiety, palpitations and weight loss.

- **Bleeding risk (see anticoagulants above):** SSRIs are associated with increased GI bleed risk. Concomitant NSAID/antiplatelets significantly increase bleed risk. Consider risk factors: age, GI history, medicines, and gastro-protection if required[3,7] Lansoprazole/omeprazole capsules NHSGGC preferred.
- **Falls risk:** Increased risk for elderly: TCAs having the highest risk followed by SSRIs and mirtazapine. Higher SSRIs doses are associated with a three-fold increase in falls risk.
- **Hyponatraemia:** Characterised by dizziness, nausea, lethargy, confusion, cramps, seizures, is associated with most antidepressants; peak onset with 30 days of starting treatment (Appendix 4). Consider monitoring at baseline, 2 and 4 weeks, and then 3 monthly.[8]
- **Sexual dysfunction:** Is usually under reported. Consider asking patients if this is problematic (Appendix 4). Both depression and antidepressants can cause disorders of desire, arousal and orgasm. If problematic consider dose reduction, switching (CKS Switching), or stopping (Appendix 3).
- **Suicide and antidepressants:** There is a slight increased risk of suicide when initiating antidepressants, especially in ≤30 year old (Appendix 4). The benefits of antidepressant outweigh the risk for their licensed indications. TCAs (excluding lofepramine) and venlafaxine have greater risk of death in overdose.
- **Weight changes** may be experienced by patients with antidepressant use (Appendix 4).

Managing adverse effects:

- Where appropriate give patient permission to stop the drug causing side effects e.g. akasthisia, aggression, etc.
- Dose reduction may help where tolerance to the adverse effect does not develop e.g. sexual dysfunction, insomnia or hypersomnia.
- Switching antidepressant to one with potentially less side effects.
- Drug holidays or cessation may also be considered as an option.

Other links which may be useful:

Choice and Medication British Association for Psychopharmacology
NICE NG 222. Depression in adults: treatment and management
NICE CG91 Depression in adults with a chronic physical health problem: Recognition and management

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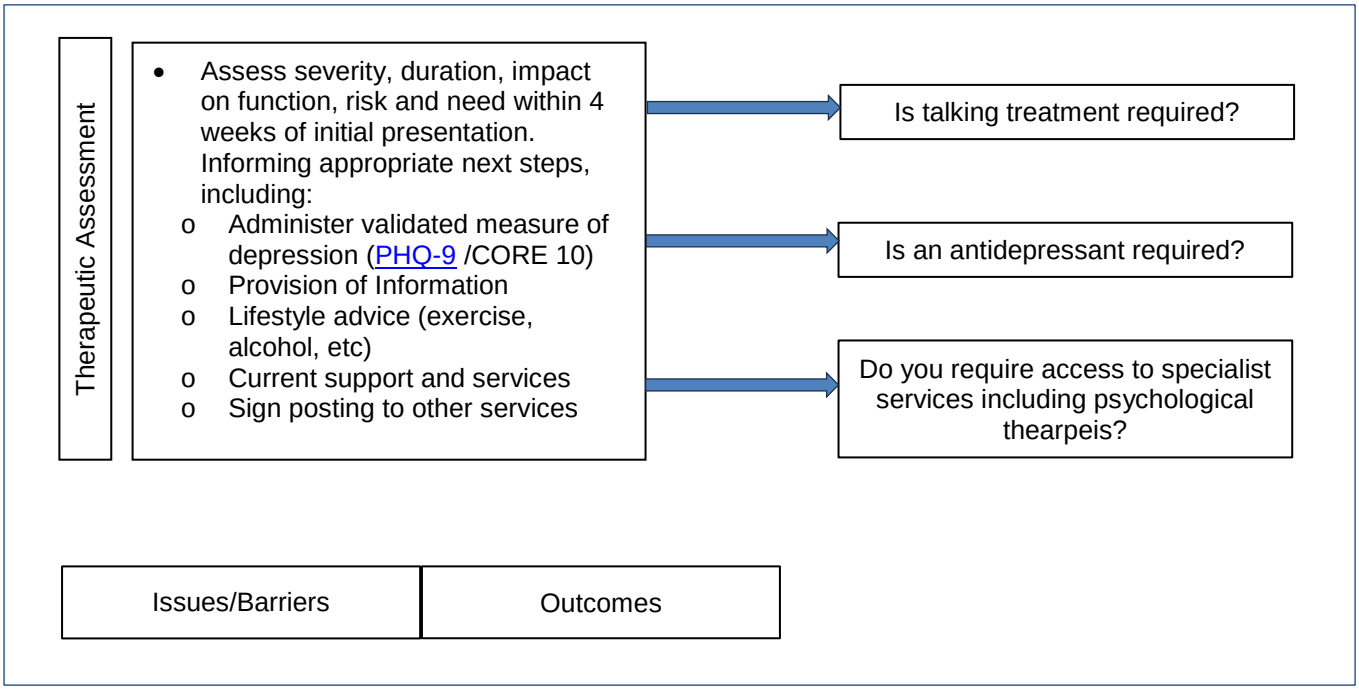
3. Cleare A, Pariante CM, Young AH, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: A revision of the 2008 British Association for Psychopharmacology guidelines. J Psychopharmacol 2015;29(5):459-525. doi: 10.1177/0269881115581093
4. Furukawa TA, Salanti G, Cowen PJ, et al. No benefit from flexible titration above minimum licensed dose in prescribing antidepressants for major depression: systematic review. Acta Psychiatrica Scandinavica 2020;141(5):401-09.
5. Furukawa TA, Cipriani A, Cowen PJ, et al. Optimal dose of selective serotonin reuptake inhibitors, venlafaxine, and mirtazapine in major depression: a systematic review and dose-response meta-analysis. Lancet Psychiatry 2019;6(7):601-09. doi: https://doi.org/10.1016/S2215-0366(19)30217-2
6. Johnson CF, Maxwell M, Williams B, et al. Dose-response effects of selective serotonin reuptake inhibitor monotherapy for the treatment of depression: systematic review of reviews and meta-narrative synthesis. BMJ Medicine 2022;1(1):e000017. doi: 10.1136/bmjmed-2021-000017
7. Taylor DM, Barnes TRE, Young AH. The Maudsley Prescribing Guidelines in Psychiatry. 14th ed. Chichester: Wiley Blackwell 2021.
8. National Institute for Health and Care Excellence. National Guideline 222: Depression in adults: treatment and management, 2022.
9. National Institute for Health and Care Excellence. Clinical Guideline 91: Depression in adults with a chronic physical health problem: recognition and management, 2009.

Appendix 1. Integrated care pathway (Return)



Appendix 2. Mental Health Support Resources and Information (Return)

Other services may be available in your area.

Helplines	Service	Contact information	Opening hours
	NHS 24	111	24 hour
	Samaritans	116 123	24 hour
	Child Line	0800 11 11	24 hour
	Scottish Domestic Abuse and Forced Marriage Helpline (For anyone affected by domestic abuse)	0800 027 1234	24 hour
	Breathing Space	0800 83 85 87	Mon to Thurs 6pm-2am, Fri 6pm to Mon 6am
	Saneline	0300 304 7000	4.00pm-10.00pm Daily
	Rape Crisis Scotland (For anyone affected by sexual violence)	08088 01 03 02	5 pm-Midnight
	Parent line Scotland (For anyone caring for or concerned about a child)	0800 028 22 33	Mon-Fri 9am-9pm, Sat-Sun, 9am to 12pm

Other Support	Service	Contact information		Opening hours
	Scottish Association for Mental Health (SAMH)	0141 530 1000	www.samh.org.uk	Mon-Fri 9am to 5pm
	Lifelink (Counselling & Resources)	0141 552 4434	www.lifelink.org.uk/	Mon - Fri 9am -5pm
	Living Life : Guided self- help and Cognitive Behavioural Therapy (CBT) telephone service	0800 328 9655	www.breathingspace.scot/living-life	Mon-Fri 1pm -9pm
	Scottish Care and Information on Miscarriage	0141 552 5070	www.miscarriagesupport.org.uk	Sometimes answer machine - can leave contact detail for a phone back
	Relationship Scotland	0345 119 2020	www.relationships-scotland.org.uk	Mon-Fri 9.30am to 4.30pm
	Family Mediation West of Scotland	0141 332 2731	https://familymediationwest.scot/	Monday to Friday 9am to 5pm
	Relationship Scotland Counselling Services	0141 248 5249	Glasgow Relationships Counselling Services (rsglasgow.org.uk)	Monday to Friday 9:30am to 8:30pm, Saturday 10am to 1pm
	Glasgow Council on Alcohol	0141 353 1800	www.glasgowcouncilonalcohol.org	Mon-Thur 9am-9pm, Fri and Sat 9am-5pm,
	Al-Anon (For anyone affected by someone else's drinking)	0800 0086 811	www.al-anonuk.org.uk	10am- 10pm daily
	Cruse Bereavement Care Scotland	08088026161	www.crusescotland.org.uk	Monday to Friday 9am - 8pm, weekends 10am - 2pm.
	Know the Score (Drug use and addiction)	0800 587 5879	www.knowthescore.info/	Mon-Fri 9am-9pm & Sat-Sun 10am-4pm
	Gamblers Anonymous Scotland	0370 050 8881	www.gascotland.org/	24 hour

Online Support

Self-help	Service		Link
	Living Life to the Full	Support Information	www.llttf.com
	Action on Depression	Support Information	Self Help Resources - Get Self Help | Lanarkshire | Element
	Wellbeing Glasgow	Support Information	www.wellbeing-glasgow.org.uk
	NHS Inform Mental Health and Wellbeing	Support information	https://www.nhsinform.scot/illnesses-and-conditions/mental-health
	Silvercloud	Range of online educational programmes to support wellbeing, stress and mild to moderate anxiety and low mood. Self or GP referral. Password: Scotland2020	SilverCloud. Making Space For Healthy Minds (silvercloudhealth.com)
	Sleepio	Online resource for Insomnia	Onboarding Sleep Test - Sleepio
	Daylight	Online resource for Anxiety	Daylight | Suitability (trydaylight.com)
Other support	Wellbeing-Glasgow-Help	Provides contact details and information on mental health and non-mental health services	Glasgow | Wellbeing Services | NHS (wellbeing-glasgow.org.uk)
	NHS Choices	Support Information	www.nhs.uk/pages/home.aspx
	Citizens Advice	Information and advice to resolve money, legal and other problem	www.cas.org.uk
Apps	Headspace	Guided meditation and Mindfulness. Advice, tips and tools to let go of stress, to help relaxation and improve sleep.	www.headspace.com
	WellMind	Advice, tips and tools to improve your mental health and boost your wellbeing	WellMind – available on App Store and Google Play

Antidepressants: Information which may be of use to patients, carers and family

- Have realistic expectations. You will still have bad days and setbacks.
- Antidepressants are not addictive.
- Any thoughts of self-harm please contact your practice, out-of-hours service (NHS 24, Tel: 111), friend or a family member.
- You may feel benefit when first starting an antidepressant, but it can take 2 to 4 weeks to provide its full effect.
- If symptoms are not improving, the antidepressant or antidepressant dose might have to be changed.
- You should take your antidepressant for at least 6 months after you feel better. If you have had 2 or more depressive episodes in the recent past, the antidepressant may be continued for up to 2 years.
- Side effects can be short lived and reduce within a few weeks of starting an antidepressant.
  - Selective serotonin re-uptake inhibitors (SSRIs) such as citalopram, fluoxetine, sertraline: nausea, vomiting, diarrhoea, anxiety, weight loss/gain, headache, insomnia. Agitation is a common side effect associated with starting and increasing SSRIs doses which normally resolves within 7-10 days, but can contribute to suicidal ideation. If this occurs,please contact your practice.
  - Tricyclic antidepressants (lofepramine, amitriptyline, etc): dry mouth, constipation, drowsiness, dizziness, increased appetite, weight gain, confusion.
  - Mirtazapine: sedation (especially at lower doses: 15mg daily), increased appetite, weight gain.
  - Trazodone: sedation, headache, nausea, vomiting, hypotension, prolong erection of the penis.
  - Venlafaxine: constipation, nausea, vomiting, weight loss, palpitations, hypertension.

  If side effects continue or are troublesome please discuss alternative treatment options with your GP.
- Discontinuation symptoms may occur on stopping, missing doses or when reducing the dose; these are usually mild and self-limiting but can be severe when antidepressants are stopped abruptly. When considering stopping antidepressants please discuss with your GP or other healthcare professional to ensure appropriate managed reduction and stopping.
- More medicines information is available at NHS Choices Antidepressants and Choice and Medication
- Avoid alcohol and recreational drugs, as can worsen depressive symptoms.
- Self-help: as outlined above and healthy reading section in local libraries.
- For the first episode of depression, the majority of people will experience remission within 6 to 12 months.
- Have realistic expectations. You will still have bad days and setbacks.

Appendix 3. Reducing and Stopping Advice (Return)

All classes of antidepressants can cause discontinuation/withdrawal symptoms, especially when stopped abruptly. Withdrawals may also occur to a lesser extent when doses are missed or reduced. Previous reports indicate that that up to 12% of people receiving placebo and up to 32-56% of people receiving different antidepressants may be affected by withdrawals.

Some people may be more sensitive to withdrawals than others, and unfortunately it is difficult to know who will or will not experience withdrawal effects. This advice is intended to provide prescribers and patients with a range of options to appropriately support and enable successful antidepressant reduction and discontinuation.

Discontinuation symptoms or 'withdrawal effects'?

The term 'discontinuation symptoms' is used to describe symptoms experienced on stopping medicines that are not drugs of dependence, although there are important semantic differences in the terms 'discontinuation' and 'withdrawal' symptoms – the latter implying addiction, the former does not. While the distinction is important for precise medical terminology, it is irrelevant when it comes to personal experiences and how an individual may describe their signs and symptoms.

- **Optimum rate of taper to prevent withdrawals is unknown.** Therefore, the prescriber and individual should discuss and agree the most appropriate approach to reducing the dose and reviewing progress.

- **Duration of reduction.**
  - ≤9 months antidepressant treatment. Reducing over 4-6 weeks may be appropriate for most individuals. However some may need longer.
  - >9 months antidepressant treatment. Slower reduction over a period of months may be required, especially for people that are anxious/distressed about reducing and/or stopping.

- **Experience significant or unbearable withdrawal effects?** Increase back to the previous dose that did not cause withdrawals, stablise, and then considering a slower rate of reduction may help.

- **Paroxetine and venlafaxine**, are more commonly associated with withdrawals. In general, higher antidepressant doses and longer duration of treatment with other antidepressants may be associated with a higher risk of withdrawals.

1. Considerations for reducing and/or stop antidepressants

Consider the clinical situation when reviewing and discussing reducing/stopping antidepressants. Encourage individuals' to discuss stopping with their prescriber before doing so. By discussing and planning withdrawals, the most appropriate rate of reduction can be agreed. Individual's experiencing serious adverse effects (Table 1) may require rapid discontinuation e.g. (<7 days).

Figure 1. Reducing and stopping antidepressants

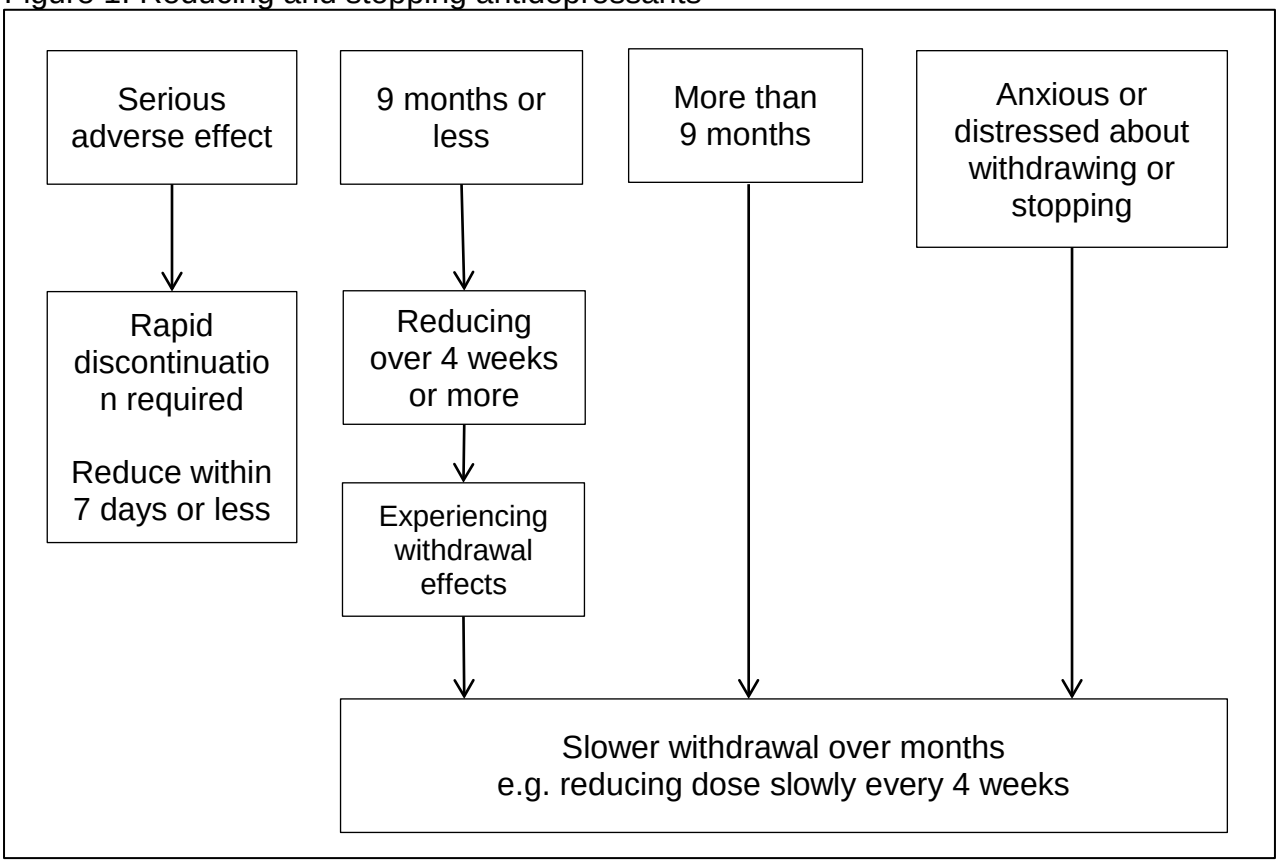


Table 1. Serious adverse effects which may require rapid discontinuation

Adverse effect	Drugs	Symptoms/Signs
Serotonin syndrome (very rare)	SSRI, SNRI, clomipramine, moclobemide, and other medicines e.g. triptans, tramadol, fentanyl, etc.	**Mild** (patient may/may not be concerned): insomnia, anxiety, nausea, diarrhoea, hypertension, tachycardia, hyper-reflexia. **Moderate** (causes distress): agitation, myoclonus, tremor, pupil dilation, flushing, sweating, low fever (<38.5°C) **Severe** (medical emergency): severe hyperthermia, confusion, rigidity, respiratory, coma, death
QTc interval prolongation	Citalopram, escitalopram, TCAs, and other medicines e.g. quinine, methadone, antipsychotics, antibiotics etc.	ECG changes in QTc interval

Note: Serotonin syndrome, for more detail see Buckley et al 2014 and Isbister 2007, QTc prolongation is of concern as it is associated with ventricular tachycardia and sudden cardiac death, see Kallergis et al 2012 and QT prolongation information.

2. Discontinuation/withdrawal symptoms

These may begin within a few days of stopping an antidepressant, and generally subside within 7-10 days, but a minority of people may experience severe or prolonged symptoms (Table 2).

Table 2. Antidepressant discontinuation/withdrawal symptoms

Antidepressant class	Most commonly associated[a]	Symptoms[b]	
		Common	Occasional
SSRI, Clomipramine (TCA)	Paroxetine	Flu-like symptoms (chills, myalgia, excess sweating, nausea, headache), 'shock like' sensations, dizziness exacerbated by movement, insomnia, excess (vivid) dreaming, irritability, crying spells	Movement disorders, concentration, memory difficulties
SNRIs	Venlafaxine	Same as above, due to serotonin effects	Same as above
TCAs	Amitriptyline, Imipramine	Flu-like symptoms, insomnia, excess dreaming. *Anticholinergic rebound* – more common in the elderly: headache, restlessness, diarrhoea, nausea and vomiting	Movement disorders, mania, cardiac arrhythmias.
Other	Mirtazapine[c]	Anxiety, panic attacks, insomnia, irritability, nausea	
	Agomelatine		Very low risk[d]
	Trazodone		Rarely SSRI type withdrawals[e]
	Vortioxetine		Unclear[d]

a. Although most commonly associated with the listed medicines, other medicines in the group may cause similar symptoms.
b. Symptoms: As individuals may or may not experience discontinuation/withdrawal symptom, and the intensity and range of symptoms may vary by individual, people may experience or identify symptoms not listed above.
c. Limited data: mirtazapine case studies, see Cosci et al 2017.
d. Agomelatine associate with very low risk, and vortioxetine risk unclear, see Henssler et al 2019.
e. See Haddad et al 2001. and Otani et al 1994. for more detail.

3. Standard reduction approaches

Appropriate for patients taking antidepressants that have no past history of distressing withdrawal, and no particular fear of withdrawing and/or stopping antidepressants over 4 to 6 weeks.

Review and reduce dose every 1 to 4 weeks or as guided by the individual's needs and/or preferences. However, reducing every 4 weeks may be more practical for individuals due to their carer, family and work commitments, as well as for collecting prescriptions and enabling appropriate face-to-face or phone review follow up.

3.1 Selective serotonin reuptake inhibitors (SSRI)

Due to the long half-life, the following can be stopped at standard daily doses: citalopram 20mg, escitalopram 10mg, fluoxetine 20mg and sertraline 50mg per day. However, individuals may prefer or require a slower reduction with lower doses.

SSRIs	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Citalopram	40mg	30mg	20mg	10mg	Stop	
Escitalopram	20mg	15mg	10mg	5mg	Stop	
Fluoxetine	40mg	30mg*	20mg	10mg**	Stop+	
Fluvoxamine	300mg	200mg	100mg	50mg	Stop	
Sertraline	200mg	150mg	100mg	50mg	25mg‡	Stop
Paroxetine†	40mg	30mg	20mg	10mg	5mg	Stop

Steps: the rate of withdrawal will vary with individual's needs e.g. weekly to 4 weekly reductions for some.
All doses are single daily doses
*Alternate day dosing 40mg/20mg
**Alternate day dosing with 20mg capsule, or consider using fluoxetine liquid
+ Consider risk of interactions for 2 weeks after stopping
‡ 25mg sertraline tablet
† Some people may require to be switched to an alternative SSRI if experiencing significant withdrawals, (section 4)..

3.2 Serotonin and noradrenaline reuptake inhibitors (SNRI)

Most individuals will be able to slowly withdraw and discontinue duloxetine and venlafaxine without any adverse effects. Where individuals experience discontinuation/withdrawal effects after stopping, it may be appropriate to restart the antidepressant at the previous dose and frequency for 7 days then switch to a long acting SSRI, interactions and contra-indications allowing (section 4).

SNRI	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6
Duloxteine[a]	120mg	90mg	60mg	30mg	Stop	
Venlafaxine MR[b]	300mg	225mg	150mg	75mg	37.5mg	Stop
Venlafaxine[c]	150mg twice daily	150mg morning 75mg night	75mg twice daily	37.5mg twice daily	Stop[d]	

Steps: the rate of withdrawal will vary with individual's needs e.g. weekly to 4 weekly reductions for some.
Note: Venlafaxine 300mg daily used as example, as individuals on higher doses are usually under the care of community mental health teams who should be involved in decisions to reduce or withdraw.

a. BNF only has 60mg dose listed for treatment of major depressive order, but duloxetine SmPC (data sheet) quotes up to 120mg daily.
b. If receiving modified release (MR) preparations as split dose e.g. twice daily, please consider that MR preparations are intended as once daily preparations.
c. Some individuals may have a preference for reducing the night-time or morning dose first.
d. Ordinary release. If needed the 37.5mg MR daily could be used for another step before stopping.

3.3 Tricyclic antidepressants (TCAs) (Return to top)

Older adults and more frail individuals may require and need slower reduction, due to risk of cholinergic rebound (nausea, vomiting, headache, restlessness). Therefore slow reduction over longer than 6 weeks, or months, may be needed for some individuals depending on their preference and/or needs.

TCAs	Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 7	Step 8
Amitriptyline[a]	150mg	100mg	50mg	Stop				
Amitripyline[a,b]	150mg	125mg	100mg	75mg	50mg	25mg	10mg[c]	Stop
Lofepramine[d]	210mg	140mg	70mg	35mg[e]	Stop			

a. The same reduction schedule would be advised for:

Clomipramine	Dosulepin (dotheipin)	Doxepin
Imipramine	Nortriptyline	Trimipramine

b. Older adults and some individuals may require reductions using smaller dose increments to minimise the risk of adverse withdrawal effects.
c. Dosulepin and doxepin not available as 10mg dose, therefore consider if necessary using 25mg capsules on alternate days, then stop.
d. If dose is split morning and night, consider reducing and stopping morning dose first, and then continuing reduction with night time dose.
e. Tablets are less suitable for halving as they have a film coating. If necessary, a 35mg dose can be given using lofepramine 70mg/5ml oral suspension.

3.4 Other antidepressants and monoamine oxidase inhibitors (MAOIs)

Other		Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	Step 7
Agomelatine		50mg	25mg	Stop				
Mirtazapine		45mg	30mg	15mg[a]	Stop			
Trazodone		300mg[b]	250mg	200mg	150mg	100mg	50mg	Stop
Vortioxetine		20mg	10mg	Stop				
Isocarboxazid[c]	Morning	60mg	50mg	40mg	30mg	20mg	10mg	Stop
Moclobemide[d]	Morning	300mg	300mg	150mg	150mg	Stop		
	Night	300mg	150mg	150mg	Stop			
Phenelzine[c]	Morning	30mg	30mg	30mg	15mg	15mg	15mg	Stop
	Afternoon	30mg	15mg	15mg	15mg	Stop	Stop	
	Night	30mg	30mg	15mg	15mg	15mg	Stop	
Tranylcypromine[c]	Morning	30mg	20mg	10mg	Stop			

Steps: the rate of withdrawal will vary with individual's needs e.g. weekly to 4 weekly reductions for some.
a. Some people may find the 15mg dose more sedating than higher doses due more antihistamine effects.
b. For higher doses consider reducing at each step by 50mg. However, clinical need and/or individual's preferences may require larger reduction steps e.g. 100mg.
c. Isocaboxazid, phenelzine and tranylcypromine inhibit monoamine oxidase A and B for up to 2 weeks after stopping. **Consider risk of interactions for 2 weeks after stopping.**
d. Moclobemide is a reversible inhibitor of monoamine oxidase A.

4. Difficulty withdrawing SSRI/SNRI or fearful

For individuals who have had or are having difficulty withdrawing and stopping short half-life antidepressants: paroxetine, venlafaxine or duloxetine. Switching to a longer half-life SSRI may enable reduction and stopping, as venlafaxine and duloxetine act as SSRIs at low doses.

Convert to long-acting SSRI and stop
Reduce the total daily dose in a stepwise fashion to: paroxetine 20mg, venlafaxine 75mg, duloxetine 30mg daily (see 3.1 SSRIs and 3.2 SNRI). Then convert to an approximate dose equivalent* of fluoxetine, citalopram or sertraline (Step 1), using standard capsules, tablets or liquid, and stabilise on that dose for 3-7 days then stop.

For example, duloxetine 30mg daily changed to fluoxetine 20mg daily and continued for 3-7 days then stopped.

Convert to long acting SSRI and reduce slowly
As some individuals may prefer or need slower reductions.

Daily dose		Step 1*	Step 2	Step 3	Step 4	Step 5	Step 6
Duloxetine 30mg Or Paroxetine 20mg Or Venlafaxine MR 75mg (37.5mg twice daily)	To any of these SSRIs	Fluoxetine 20mg	20mg alternate days	20mg every third day	Stop+		
		Citalopram 20mg	10mg	10mg alternate days	Stop		
		Sertraline 50mg	25mg	12.5mg	Stop		
		Fluoxetine liquid[a,b,c] (20mg in 5ml)	16mg (4ml)	12mg (3ml)	8mg (2ml)	4mg (1ml)	Stop

Steps: the rate of withdrawal will vary with individual's needs e.g. weekly to 4 weekly reductions for some.
* Approximate dose equivalents
+ Consider risk of interactions for 2 weeks after stopping

a. Some community pharmacies may not stock 1ml graduated 5ml oral syringes, but they can order these if given some warning.
b. Citalopram 40mg/ml and escitalopram 20mg/ml liquid are not recommended due to the difficulty with accurately measuring small doses.
c. Sertraline liquid is not recommended as it is unlicensed in the UK, and individuals may experience oral numbness on their tongue and mouth due to the anaesthetic effects of non-tablet formulations. Sertraline Prescribe and half 25mg sertraline tablets if needed.

*Approximate dose equivalents and switching considerations:

- Due to inter-patient variability and differing half-lives, this means that these are approximate dose equivalents, not exact equivalence.
- The drug and dose equivalents can never be exact, and should be interpreted considering your clinical knowledge and the individual patient's needs.
- Drug interactions and drug-disease interactions.

5. Significant difficulty or fears withdrawing SSRI/SNRI

For a very small minority of individuals, slower graduated reduction may be appropriate:
- Where standard reduction (SSRI section 3.1 or SNRI section 3.2) and/or
- Difficulty discontinuing/withdrawing SSRI/SNRI (section 4),

have been tried and are unsuccessful. This approach may help flatten the reductions in plasma drug concentrations at lower doses (Figure 2).

First, reduce current antidepressant to standard dose as per SSRI 3.1 or SNRI 3.2. Then convert to an approximate dose equivalent of fluoxetine 20mg/5ml liquid.

Fluoxetine 20mg is approximately dose equivalent* to:
- Citalopram 20mg
- Escitalopram 10mg
- Fluvoxamine 50mg
- Paroxetine 20mg
- Sertraline 50mg
- Duloxetine 30mg
- Venlafaxine 75mg

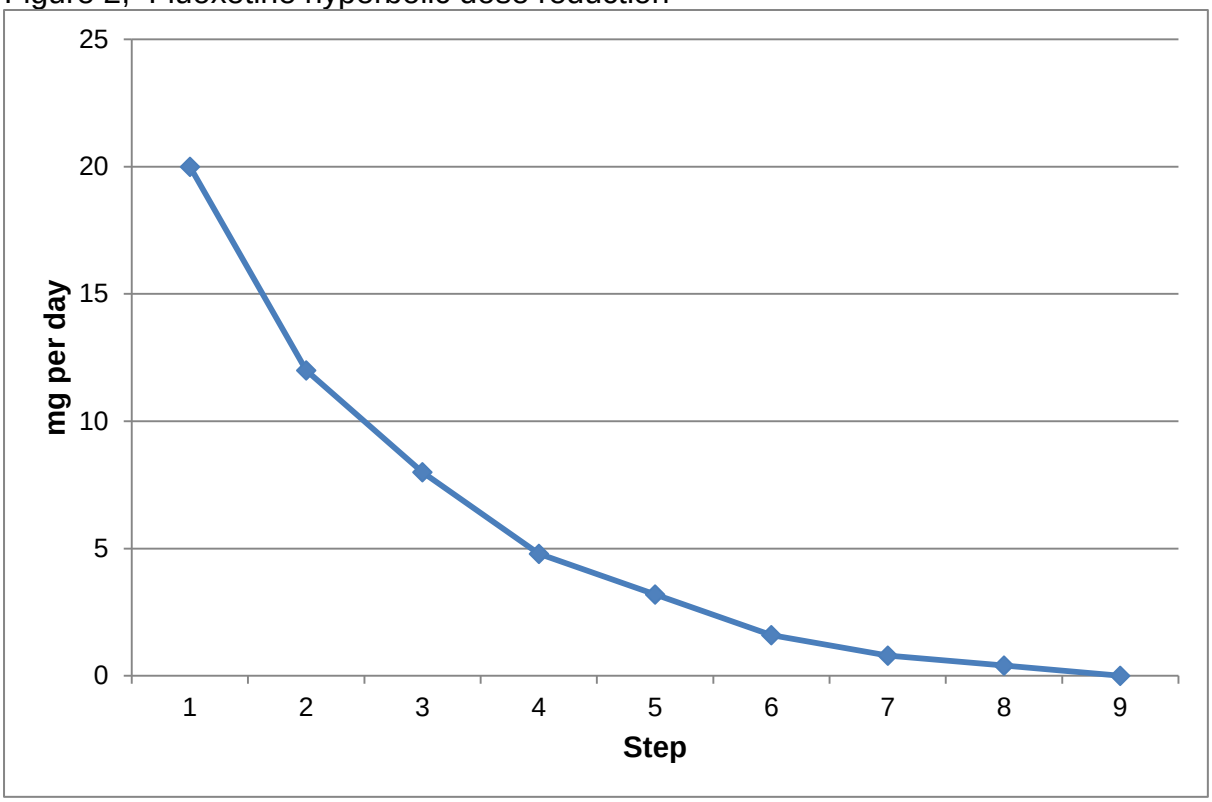
***Approximate dose equivalents and switching considerations:**
- Due to inter-patient variability and differing half-lives, this means that these are approximate dose equivalents, not exact equivalence.
- The drug and dose equivalents can never be exact, and should be interpreted considering your clinical knowledge and the individual patient's needs.
- Drug interactions and drug-disease interactions.

For example: paroxetine 20mg daily to fluoxetine 20mg daily, or paroxetine 10mg daily to fluoxetine 8mg daily (Step 3 below). Switch by taking last dose of paroxetine today and starting new dose of fluoxetine tomorrow at the same time of day. Agree an appropriate rate of reduction e.g. weekly or monthly, agree face-to-face or phone review follow up.

Fluoxetine liquid 20mg/5ml			
Step	**mg/d**	**ml/d**	**Step down Difference (mg)**
1	20	5	
2	12	3	8
3	8	2	4
4	4.8	1.2	3.2
5	3.2	0.8	1.6
6	1.6	0.4	1.6
7	0.8	0.2	0.8
8	0.4	0.1	0.4
9	Then stop	0	0.4

Note:
- Steps: the rate of withdrawal will vary with individual's needs e.g. weekly to 4 weekly reductions for some.
- Citalopram 40mg/ml and escitalopram 20mg/ml liquid are not recommended due to the difficulty with accurately measuring small doses.
- Sertraline liquid is not recommended as it is unlicensed in the UK, and individual's may experience oral numbness on their tongue and mouth due to the anaesthetic effects of non-tablet formulations

Figure 2, Fluoxetine hyperbolic dose reduction



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Appendix 4. Adverse effects (sexual dysfunction, suicide and weight gain) (Return)

Hyponatraemia: Higher risk with one or more of the following: previous hyponatraemia, elderly (>80 years), female, low body weight, reduced renal function (GFR <50ml/min), co-morbidities (hypothyroid, diabetes, COPD, hypertension, stroke, etc) and other medicines (diuretics, carbamazepine, NSAIDs, antipsychotics, tramadol, omeprazole or trimethoprim). Switching antidepressant to a different class may be effective

Sexual dysfunction: Severity increases with severity of depression. Antidepressant induced sexual dysfunction is commonly under reported (3-8% of patients spontaneously reporting such side effects and 34-75% reporting side effects on direct questioning[1]) with patient presenting with a variety of side effects: reduced libido, arousal dysfunction and orgasmic disorders.[1-3] Antidepressant induced sexual dysfunction spontaneously remits in approximately 10% of cases with partial remission in a further 11%. Effects are usually reversible, however some people may experience long-lasting sexual dysfunction despite SSRI/SNRIs being discontinued.[3]

Consider other causes such as alcohol, benzodiazepines, beta-blockers, co-morbidity, relationship difficulties, etc. Spontaneously remits for 10% and partially remits for 11%. If this does not occur consider dose reduction, switching or discontinuing antidepressant where appropriate.

Antidepressant	Approximate prevalence of sexual dysfunction
Venlafaxine	70%
SSRIs	60-70%
Duloxetine	46%
Tricyclic antidepressants	30%
Mirtazapine	25%
Placebo	14%
Trazodone	Unknown
Adapted from Maudsley 2015[4] and Serretti & Chiesa 2009[1]	

Suicide, akasthisia and aggression: Akasthisia or restless over activity may be experienced by some patients when initiating or increasing SSRI doses is usually short lived (settles within the first 10 days), but can contribute to suicidal ideation.[5-7] Under 30 year olds being at higher risk of suicidality associated with a variety of antidepressants.[7] Aggressive behaviours are also associated with antidepressant use with greatest associated risk being observed for children and adolescents (<18 years old).[8] If this occurs, advise patient to contact the practice for advice or consider giving prior advice to stop and attend for review if appropriate.

Weight changes: Patients may experience weight changes during antidepressant treatment. Weight gain may be associated with depression recovery and improved appetite on one hand and undesirable antidepressant effects on the other.[9] However, many placebo controlled studies report no weight data making it difficult to accurately estimate weight changes.[2] SSRIs have been seen as weight neutral, or in some cases associated with weight loss in the short-term (≤8wk studies) and weight gain in the long-term.[9]

Antidepressant	% Patient with Weight gain
Amitriptyline	22%
Imipramine	13.3%
Mirtazapine	12.7%
Fluoxetine	4.8-6.8%
Sertraline	4.2%
Citalopram	3.9%
Placebo	2.6-6.3%
Venlafaxine	Weight loss.
Weight gain can vary from 0.5-1kg with SSRIs[9 10] to 2.5-3.3kg with mirtazapine[11] Summarised from review articles[2 9 10]	

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