DERBYSHIRE JOINT AREA PRESCRIBING COMMITTEE (JAPC)

Derbyshire Healthcare NHS Foundation Trust

Antidepressants in unipolar depression

Guidelines for selecting and reviewing antidepressants in adults aged 18 or over, including older people

What NICE NG222 says:

	Description	How are antidepressants used initially	Considerations	Other options
Less severe depression	Encompasses subthreshold and mild depression, and in NG222 is defined as depression scoring <16 on the PHQ-9 scale	Do not routinely offer antidepressant medication as first-line treatment unless that is the person's preference A course of **SSRI** medication can be considered Usually take for at least 6 months (and for some time after symptoms remit)	Minimal time commitment, although regular reviews needed, especially when starting or stopping treatment Benefits should be felt within 4 weeks There may be side effects from the medication and some people may find it difficult to later stop antidepressant medication See NG222 recommendations on starting and stopping antidepressant medication for more details	Guided self-help Group CBT Group BA Individual CBT Individual BA Group exercise Group mindfulness and meditation Interpersonal psychotherapy Counselling Short-term psychodynamic psychotherapy
More severe depression	Encompasses moderate and severe depression, and in NG222 is defined as depression scoring 16 or more on the PHQ-9 scale	Can be **SSRI**, **SNRI**, or **other antidepressant if indicated** based on previous clinical and treatment history Usually take for at least 6 months (and for some time after symptoms remit) SSRIs are generally well tolerated, have a good safety profile and should be considered as the first choice antidepressant for most people TCAs are dangerous in overdose, although lofepramine has the best safety profile Choice of treatment will depend on preference for specific medication effects such as sedation, concomitant illnesses or medications, suicide risk and previous history of response to antidepressant medications		CBT + antidepressant Individual CBT Individual BA Individual problem-solving Counselling Short-term psychodynamic psychotherapy Interpersonal psychotherapy Guided self-help Group exercise
Chronic depressive symptoms	Includes those who continually meet criteria for the diagnosis of a major depressive episode for at least 2 years, or have persistent subthreshold symptoms for at least 2 years, or who have persistent low mood with or without concurrent episodes of major depression for at least 2 years	A course of **SSRI** or **SNRI** medication For people with chronic depressive symptoms that significantly impair personal and social functioning, who have not responded, consider alternative medication in specialist settings or after consulting a specialist. Alternatives include TCAs, moclobemide, irreversible MAOIs such as phenelzine, low dose amisulpride (max 50mg daily)		CBT CBT with either an SSRI or TCA

Adapted from NICE NG222 (2022)

Choosing an antidepressant medicine

Step 1

Choose from:
- **SSRI** at standard dose (consider sertraline if MI in past 4 weeks, unstable angina or QT prolongation risk)
- **Venlafaxine (**only for more severe or chronic depression)

Consider **Mirtazapine** as alternative to SSRI if high risk of bleed (esp GI) or concurrent NSAID, antiplatelet, anticoagulant or corticosteroid.

Do not routinely offer antidepressant medication as first-line treatment for **less severe depression** unless that is the person's preference

Ineffective or not tolerated

Step 2

Choose from:
- Increase dose within licensed dose range
- Alternative **SSRI**
- **Venlafaxine** if not already tried
- **Trazodone**
- Re-start **TCA** if not contra-indicated and previously effective and tolerated (not dosulepin/trimipramine)

For advice on **switching antidepressants**, refer to the NICE Clinical Knowledge Summary

Ineffective or not tolerated

Step 3

Re-evaluate diagnosis

Options include:
- Increase dose within licensed dose range
- Alternative from step 2
- **Vortioxetine** (only when there has been no, or limited, response to at least 2 previous antidepressants)
- **Moclobemide** (for chronic depressive symptoms)

Specialist recommendation:
- **MAOI** monotherapy (**phenelzine- specialist initiation**)
- **Tricyclic antidepressant** (not dosulepin/trimipramine)
- Low dose **amisulpride** (for chronic depressive symptoms)

Ineffective or not tolerated

Step 4

Re-evaluate diagnosis

Specialist recommendation:
- Combine antidepressants from different classes, e.g.:
  - **Mirtazapine + SSRI**
  - **Mirtazapine + Venlafaxine**
  - **Trazodone + SSRI**

Specialist initiation only:
- **Atypical antipsychotic** augmentation (follow physical health monitoring guidance in Antipsychotics – prescribing and management for mental health conditions guideline)
- **Lamotrigine** augmentation and dose stabilisation
- **Lithium** augmentation (see shared care)
- **Liothyronine** (T3) augmentation (**GREY**: Specialist initiation by consultant psychiatrist)
- Electro-convulsive therapy in addition to antidepressant medication

Materials to support conversations with patients about antidepressant choice can be found at http://www.choiceandmedication.org/derbyshcft

Starting antidepressant medication

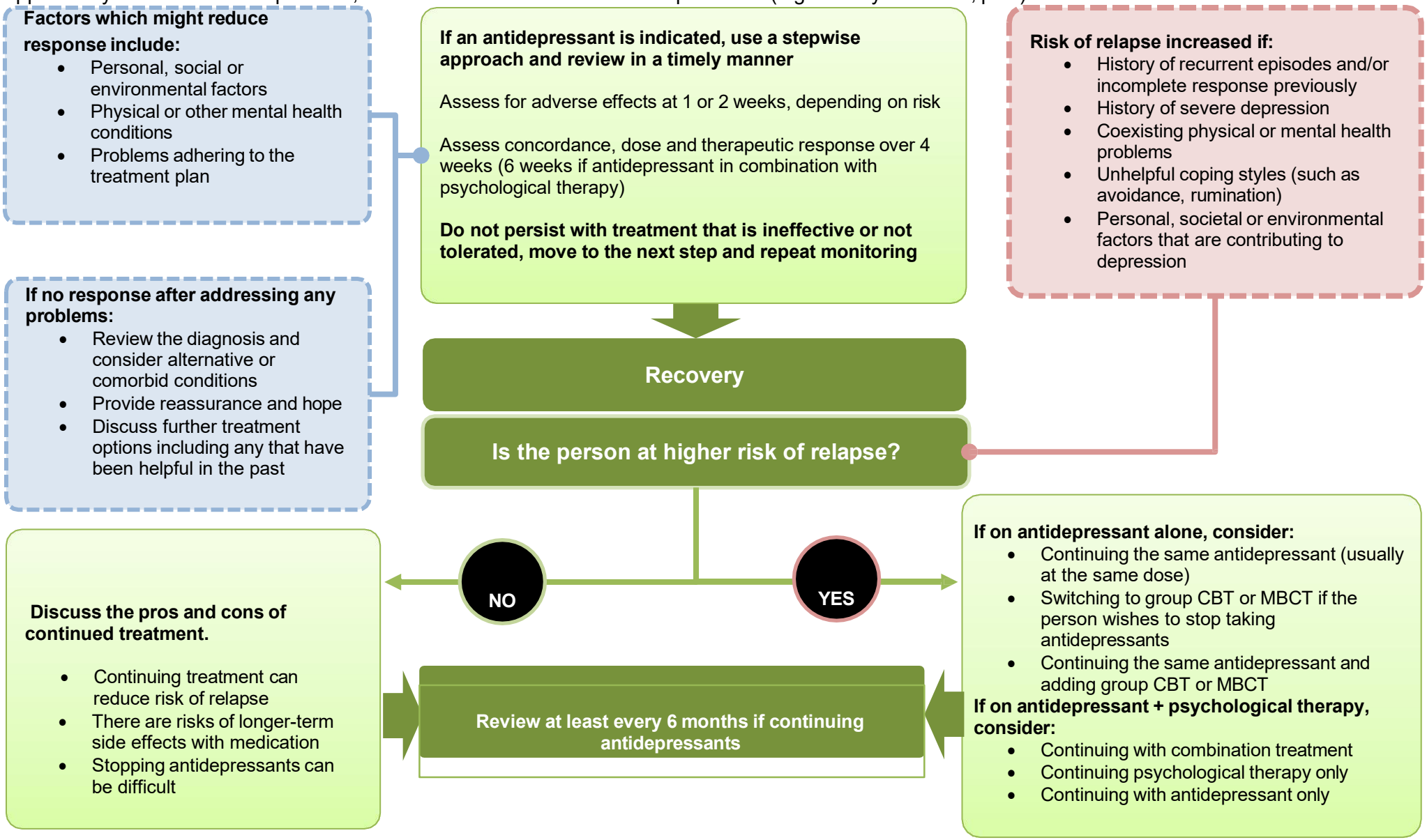
Discuss and agree a management plan with the person:	• **reasons** for offering medication • **choices** of medication (if a number are suitable) • **dose** and how the dose may need to be adjusted • **benefits**, covering what improvements the person would like to see in their life and how the medication may help • **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) • any concerns they have about **stopping the medication**

Ensure people have information about:	• How they might be affected when they first start taking antidepressant medication, and what those effects might be
	• How long it takes to see an effect (usually, if the antidepressant medication is going to work, within 4 weeks)
	• When their first review will be:
	  ○ Usually within 2 weeks to check their symptoms are improving, and for side effects
	  ○ After 1 week if a new prescription is for a person aged 18 to 25 years or of there is a particular concern for risk of suicide
	• The importance of following instructions on how to take antidepressant medication (e.g. time of day, interactions with other medicines, alcohol or food)
	• Why regular monitoring is needed and how often they will need to attend for review
	• How they can self-monitor their symptoms, and how this may help them feel involved in their own recovery
	• That treatment may need to be taken for at least 6 months after the remission of symptoms, but should be reviewed regularly
	• How some side effects might persist throughout treatment
	• Withdrawal symptoms and how these withdrawal effects can be minimised

Resources:	• NG222
	  ○ Risk assessment and management
	  ○ Antidepressant medication for people at risk of suicide
	  ○ Antidepressant medication for older people
	
	• Choice and Medication
	  ○ Antidepressant “Handy Chart” (this may include options not available in Derbyshire)
	  ○ Patient Information Leaflets

Monitoring antidepressant medication and preventing relapse

Applies only to treatment of depression, but not other clinical uses of antidepressants (e.g. anxiety disorders, pain)



Stopping antidepressant medication

When stopping someone's medication

Monitor and review people while their antidepressant is being reduced, both for withdrawal symptoms and the return of symptoms of depression. Base the frequency of monitoring on the person's clinical and support needs

- **Plan for withdrawal to take at least four weeks in most cases**
- Take into account the pharmacokinetic profile of the medicine and the duration of treatment
  - Paroxetine and venlafaxine are more likely to be associated with withdrawal symptoms so take particular care with them
- Slowly reduce the dose to zero in a step-wise fashion, at each step prescribing a proportion of the previous dose (for example 50% of previous dose)
- Consider smaller reductions (e.g. 25%) as the dose becomes lower
- If, once very small doses have been reached, slow tapering cannot be achieved using tablets or capsules, consider using liquid preparations if available
- Ensure the speed and duration of the reduction is led by and agreed with the person taking the medication, ensuring any withdrawal symptoms have resolved or are tolerable before making the next dose reduction
- Take into account the broader clinical context such as the benefit of more rapid withdrawal if there are serious or intolerable side effects (e.g hyponatraemia or upper GI bleeding)
- Take into account that more rapid withdrawal may be appropriate when switching antidepressants
- Recognise that withdrawal may take weeks or months to complete successfully

Symptoms of antidepressant withdrawal may include:

- Unsteadiness, vertigo or dizziness
- Altered sensations (e.g. electric shock sensations)
- Altered feelings (e.g. irritability, anxiety, low mood, tearfulness, panic attacks, irrational fears, confusion or very rarely suicidal thoughts
- Restlessness or agitation
- Problems sleeping
- Sweating
- Abdominal symptoms (e.g. nausea)
- Palpitations, tiredness, headaches, aches in joints and muscles

If a person has withdrawal symptoms

Reassure them they are not having a relapse of their depression. Explain that:

- These symptoms are common
- Relapse does not usually happen as soon as you stop taking an antidepressant or reduce the dose
- Even if they restart or increase the antidepressant the withdrawal symptoms may take a few days to disappear

Mild symptoms

- Monitor the symptoms
- Reassure them that such symptoms are common and usually time limited
- Advise them to contact the person who prescribes their antidepressant if symptoms do not improve, or get worse

More severe symptoms
Consider re-starting the original antidepressant at the previous dose, and then attempt dose reduction at a slower rate with smaller decrements after symptoms have resolved.

Withdrawal symptoms:

- can be mild, may appear within a few days of reducing or stopping antidepressant medication, and usually go away within 1 to 2 weeks
- can sometimes be more difficult, with symptoms lasting longer (in some cases several weeks, and occasionally several months)
- can sometimes be severe, particularly if the antidepressant medication is stopped suddenly

Other considerations:

Hyponatraemia – any antidepressant may be associated with this. Recommendation is for baseline serum sodium and repeat within first month. Risk is greater in older adults or those taking concurrent natriuretic medicines e.g. diuretics or with low body weight or in warm weather. Management- consider other cause of hyponatraemia, stop antidepressant and monitor serum sodium. Consider switching to another class e.g. from SSRI to TCAD or a MAOI or mirtazapine if appropriate.

Referral to individual antidepressant information at: www.medicines.org.uk

Antidepressant	**Risk of hyponatraemia**	**Level of evidence**
SSRI	High	Strong
SNRI	High	Strong
TCAD	Moderate	Strong
MAOI	Low	Weak
NaSSA (mirtazapine)	Low	Strong
Agomelatine	Low	Weak

** Please note this table is not exclusive and prescribers should use professional judgement for individual patients considering co-morbidities, concurrent medicines and current presentation.*

Serotonin syndrome and toxicity – This is often predictable from serotonergic drug combinations; including single serotonergic agents in highly susceptible individuals, lithium, some atypical antipsychotics and non-psychiatric medicines e.g. tramadol, sumatriptan.
A useful summary of serotonin syndrome is available from the UK Specialist Medicines Service:
https://www.sps.nhs.uk/wp-content/uploads/2018/08/UKMi_QA_Whatisserotoninsyndrome_FINAL2020.pdf

Co-morbid conditions requiring careful consideration of the choice of antidepressant include:
Diabetes, glaucoma, epilepsy, bleeding disorders (especially gastro-intestinal bleeding - see above) and cardiovascular disease (including hypertension, postural hypotension, arrhythmias, known QT prolongation, congenital QT syndrome and conditions that pose a risk of Torsade de Pointes including medication known to be associated with QT prolongation).There is perhaps a greater association of QT prolongation with Citalopram than with other SSRIs and safeguards in terms of appropriate patient selection and consideration of concomitant medication should be taken as detailed below and in the Citalopram SPC.

Cognitive Behavioural Therapy (CBT) and other intervention options

The use of antidepressants should be considered within the overall framework of managing depression where other intervention options may also be appropriate e.g. in moderate depression. CBT should also be considered for those service users who do not take, refuse or are unable to tolerate antidepressant treatments or have shown an inadequate response to them. In severe depression, a combination of antidepressants and individual CBT has been shown to be more cost effective than either treatment alone. Other options to consider are Interpersonal Psychotherapy (IPT), couple-focused therapy and occupational therapy.

Electro-Convulsive Therapy (ECT)

Should be considered as an emergency treatment in life-threatening situations. It may also be considered in severe depression where a trial of antidepressants up to and including Step 3 of the above algorithm (where feasible) has produced inadequate response or has been poorly tolerated, depending on the individual clinical situation.

Citalopram - MHRA Usage and Maximum Dose Recommendations

1. Whilst Citalopram remains a treatment option in Derbyshire, the MHRA has warned of dose-dependent QT prolongation associated with Citalopram (MHRA Drug Safety Update Citalopram and Escitalopram: QT interval prolongation Dec 2011 Vol 5 Issue 5). Therefore licensed prescribing recommendations changed in October 2011.

- Citalopram is contraindicated in people:
  - with a known QT prolongation or congenital long QT syndrome
  - taking other medicines known to prolong QT interval (see individual Summary of Product Characteristics for the relevant product at www.medicines.org.uk or check QTc risk at www.crediblemeds.org)
- Citalopram should only be used with caution in people with higher risk of developing Torsades de Pointes e.g. CHF, recent MI, bradyarrhythmias, hypokalaemia, hypomagnesaemia, other disturbances of electrolytes or concomitant illness predisposing to lengthened QT interval. A useful summary is available from the UK Specialist Pharmacy Service:
  - https://www.sps.nhs.uk/wp-content/uploads/2017/09/UKMI_QA_DruginducedQTprolongation_update_Jan2020.doc
- Citalopram should not be used above 40mg/d in adults
- Citalopram should not be used above 20mg/d in older adults and people with reduced hepatic function
- Patients on Citalopram at high risk of QT prolongation should be offered ECG monitoring.
- Patients on Citalopram should be advised to contact a health care professional immediately if they experience signs or symptoms of an abnormal heart rate or rhythm, such as fast or irregular heartbeat, shortness of breath, fainting, collapse or dizziness.

In addition, Cimetidine may inhibit the metabolism of Citalopram and caution is therefore advised when co-administering (the FDA recommend not exceeding 20mg/day for such patients).

The following flowchart provides guidance on appropriate steps when reviewing patients who are prescribed citalopram.

Citalopram Use and Maximum Dose Recommendations

NHS Derbyshire Healthcare NHS Foundation Trust

MHRA recommendations for citalopram due to a dose-dependent risk of QTc prolongation:
- Maximum dose 40mg in adults
- Maximum dose 20mg in older people
- Maximum dose 20mg in people with reduced hepatic function
- Contraindicated with known QT prolongation, congenital long QT syndrome or taking other QT-prolonging medicines
- Caution with higher risk of developing Torsades de Pointes

A QTc interval beyond 500ms is generally considered to present an unacceptable level of risk, necessitating prompt review and/or change of medicine regimen.

QTc prolongation has also been reported with other antidepressants including: all SSRIs, mirtazapine, venlafaxine and tricyclic antidepressants. If switching to one of these agents, use the minimum effective dose and consider repeat ECG monitoring

Does the patient taking citalopram have known QTc prolongation, congenital long QT syndrome, higher risk of Torsades de Pointes or concomittent QT-prolonging medication?

NO → Is citalopram above the maximum licensed dose?

NO → Continue citalopram

YES → Discuss MHRA contraindications with patient. Is there a compelling reason not to reduce the dose to one within the license?

NO → Discuss with the patient and reduce stepwise (usually over 4 weeks) to within maximum licensed dose for patient's diagnosis. Review patient within 2-4 weeks.

Patient remains clinically stable?

NO → (back to Perform ECG and check U&Es to exclude electrolyte imbalance)

YES → Perform ECG if new QT-prolonging medicines are co-prescribed and considered essential

YES → Perform ECG and check U&Es to exclude electrolyte imbalance

Is QTc ≥ 500ms?

NO → Seek psychiatrist +/- cardiologist opinion

Having obtained specialist opinion and considered other options, if it is felt to be in the patient's best interests to continue using citalopram outside of its product license, this should be discussed fully with the patient. Patient consent should be clearly documented and the prescriber takes full responsibility for unlicensed dose or off-label use. Tell patient to report heart-rhythm disturbance or fainting.

→ Repeat regular ECG monitoring, e.g. 6-monthly or after any dose or relevant medicine changes

YES → Call patient for review. Check for further risk factors such as citalopram prescribed above the licensed maximum dose. Discuss MHRA contraindications, seek patient view of switching to a suitable alternative.
Is there a compelling reason to remain on citalopram (e.g. previous treatment-resistant depression)

YES → Switch to an appropriate alternative for the given indication

NO → Perform ECG after dose stabilisation and after any relevant medicine or dose changes

Document Control	Date
Hyponatraemia and antidepressants Specialist Pharmacy Service link removed and page 6 information updated with added table.	January 2024
Link to physical health monitoring guidance added to table on page 2 and liothyronine traffic light status updated	January 2025