Depression Medication Pathway

journey to change

NHS Tees, Esk and Wear Valleys NHS Foundation Trust

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Medicines Optimisation – Interactive Guide (version for primary care here)

Quick Reference Guide

This Pathway provides guidance on the safe and appropriate use of medication for the management of depression. It is not a substitute for sound clinical decision making and should be viewed in line with national and BNF guidance.

Click on the 'buttons' on this page to navigate the document. Use "Ctrl+F" and type in keywords to quickly search the document.

Any drug marked with an **(N)** is recommended by NICE guidelines. As you move through the steps, the choices are often off-label (see Governance).

Related Guidance

The Prescribing and Initiation of Medicines procedure covers all the key aspects to consider before prescribing (internal TEWV link)

Starting Medication

The Safe Transfer of Prescribing Guidance covers key aspects of communication with GPs & broad rules of transfer of Green/All settings & Green+/Specialist Advice medicines

Communication & Transfer of Prescribing

Title	Depression Medication Pathway		
Approved by	Drug & Therapeutics Committee	Date of Approval	23 September 2026
Protocol Number	PHARM-0047-v5	Date of Review	1 October 2029

Prescribing Considerations (1)

PHARM-0047-v5

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Patient Specific Factors

Suicide Risk

- Use of antidepressants reduces suicide risk at epidemiological level; however, studies have found increased suicidal ideation following initial use, particularly in children and young adults
- Ensure regular reviews initially every 1-2 weeks. If considered high risk, limit quantities of medication (see "toxicity")
- Signpost to support services e.g. Samaritans, Papyrus, Rethink, Staying Safe, The CALM zone, Young Minds, Recovery College

Seizure Risk

- SSRIs considered low risk - Es/Citalopram as first line followed by Sertraline. Mirtazapine and Duloxetine are also low risk. Avoid TCAs.

Liver and Kidney Impairment

- Medications can accumulate due to reduced metabolism and elimination
- Doses may need reducing and titrating slower than usual
- Avoid medications with anticholinergic or QTc prolonging effects due to urinary retention and electrolyte abnormalities

Cardiac Disease

- Sertraline, Fluoxetine and Mirtazapine appear safe. See Management of QTc Prolongation

Pregnant or planning pregnancy

- Consider relative risks of mental ill health vs medication risks
- See Medication and Childbearing Potential, C&M "Drugs in Pregnancy" (internal TEWV) or Bumps

Key prescribing guidelines

- At all steps, consider non-pharmacological options instead of or in support of drug treatment, e.g. talking therapies
- Review a full list of medical problems and medication inc. OTC, non-GP medicines, illicit and herbal/homeopathic
- Consider causative underlying physical health problems, e.g. hypothyroidism
- Consider monotherapy within licensed dose range first (if tolerated)
- Medication trials should be at least 4 weeks at the maximum tolerable dose though effects can be seen as early as the first week
- If there is no improvement, consider stopping the medication and switching to an alternative treatment. Also, consider reviewing the diagnosis and differential diagnoses
- Antidepressants used for alternative indications at low doses should be taken into consideration but are not considered combination treatment
- NMPs must only prescribe within their scope of practice

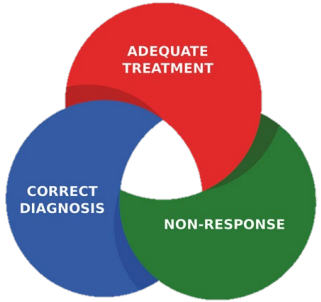
Prescribing Considerations (2)

Toxicity

- There are significant differences in toxicity (internal TEWV link) between medication classes requiring careful consideration for people with history of overdose
- TCAs have high fatality risk, except for Lofepramine
- SNRIs and most antipsychotics are slightly more toxic in overdose than SSRIs and Mirtazapine which are relatively safe options

Partial Response and Dose Response

- Antidepressant effects can be seen as early as 1-2 weeks with full effects around 4 weeks
- Consider potential causes for lack of response:
  - Accuracy of diagnosis
  - Physical or psychiatric co-morbidity
  - Adherence to treatment – 10–60% of people with depression reported poor-adherence
  - Psychosocial perpetuating factors
- Medications rarely have a linear relationship between efficacy and dose; however, adverse effects are more pronounced making progressive dose increases without adequate clinical benefit illogical
- Additionally, approximately 80% of serotonin transporter occupancy occurs at minimum therapeutic dose, making optimal doses lower than licenced maximum doses:
  - SSRIs: Fluoxetine 20-40mg/day, Sertraline 50-100mg/day, Citalopram 20-40mg/day, Escitalopram 10-20mg/day
  - Mirtazapine 30mg/day
  - Venlafaxine 150-375mg/day (noradrenergic effects 225-375mg)



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Prescribing Considerations (3)

Patient Information and Shared Decisions

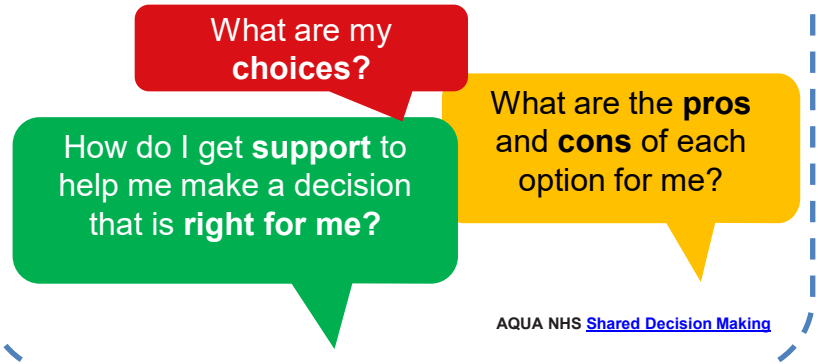
When discussing treatment consider:

- Carer involvement and views
- Patient needs and preferences
- Information is available in an accessible format and promotes patient choice (see Patient Decision Aid and Choice and Medication **Nb.** For TEWV employees or patient/carer access only)
- What the options might be if the treatment does not work

Before initiating medication explain:

- Potential side effects and whether they might improve or worsen over time
- Suicidal ideation and possible increased thoughts when offering antidepressants
- Potential for sexual dysfunction (particularly SSRIs) and that symptoms may continue after stopping treatment, known as post SSRI sexual dysfunction (PSSD).
- Risk of discontinuation symptoms, including if missing doses, and how these can be minimised (See Deprescribing)
- Any implications of taking the medicine if the person is pregnant or planning pregnancy

Encourage Patients to Ask 3 Questions



AQUA NHS Shared Decision Making

Associated Guidance

- Antidepressant Handy Hints
- Management of QTc Prolongation
- MSS36: Serotonin Syndrome

Governance (1)

Some SSRIs e.g. Paroxetine and Fluvoxamine are not recommended due to potential for withdrawal effects and interactions via CYP enzyme inhibition, respectively.

Licensing and Off-label Medicines

- Medications for licensed indications are preferred over off-label use unless these are recommended by NICE.
- Many off-label uses are supported by a sufficient evidence base and have been approved for routine use by TEWV.
- See: Guidance on Unlicensed and Off-Label Use of Medicines & Safe Transfer of Prescribing Guidance for further information.

	Licensed	NICE recommended	Locally approved
ANTIDEPRESSANTS			
SSRIs			
Citalopram	✅	✅	
Escitalopram	✅	✅	
Fluoxetine	✅	✅	
Sertraline	✅	✅	
SNRIs			
Duloxetine	✅	✅	
Venlafaxine	✅	✅	
Other Antidepressants			
Agomelatine	✅	✅	
Bupropion	❌		✅
Mirtazapine	✅	✅	
Reboxetine	✅	✅	
Vortioxetine	✅	✅	

	Licensed	NICE recommended
ANTIDEPRESSANTS		
Tricyclic Antidepressants (TCAs)		
Amitriptyline	✅	✅
Clomipramine	✅	✅
Imipramine	✅	✅
Lofepramine	✅	✅
Monoamine oxidase inhibitors (MAOIs)		
Moclobemide	✅	✅
Phenelzine	✅	✅

TCAs are more cardiotoxic (particularly in overdose) than other options and Dosulepin is not recommended. MAOIs carry dietary restrictions and should only be initiated by Consultant Psychiatrist or Level 3 NMP with appropriate competency.

- Agomelatine Primary Care Information sheets: DTVF & NYY
- Bupropion Primary Care Information sheets: DTVF & NYY

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Governance (2)

Licensing and Off-label Medicines

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- Many off-label uses are supported by a sufficient evidence base and have been approved for routine use by TEWV.
- See: Guidance on Unlicensed and Off-Label Use of Medicines & Safe Transfer of Prescribing Guidance for further information.

	Licensed	NICE recommended	Locally approved
Antipsychotics			
Amisulpride	❌	✅	✅
Aripiprazole	❌	✅	✅
Lurasidone	❌		✅
Olanzapine	❌	✅	✅
Quetiapine	✅ (MR formulations only)	✅	✅ (IR formulations)
Risperidone	❌	✅	✅
Mood stabilisers			
Lamotrigine	❌	✅	✅
Lithium	✅	✅	✅
Other medications			
Buspirone	❌		✅
Levothyroxine	❌		✅
Triiodothyronine (Liothyronine)	❌	✅	✅ (SAF required)
Ketamine (IV)	❌		✅ (SAF required)

**depressive disorder with mixed (sub-threshold hypomanic) features*

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Psychological Intervention

First Line Management

Psychological treatment (+/- medication) for depression is considered first line by NICE and many management guidelines, following a stepped care approach:

SEVERITY

Focus of the intervention	Nature of the intervention
STEP 4: Chronic depression, psychotic depression, and depression with personality disorder	Medication, high-intensity psychological interventions, ECT, crisis service, combined treatments, multiprofessional and inpatient care
STEP 3: More severe depression, or less severe depression with limited response to initial interventions	Medication, high-intensity or low-intensity psychological interventions, combined treatments
STEP 2: Less severe depression	High-intensity or low-intensity psychological and psychosocial interventions, medication
STEP 1: All known and suspected presentations of depression	Assessment, referral, psychoeducation, active monitoring and support



Talking therapies in County Durham and Darlington

NHS Durham and Darlington Talking Therapies

Talking therapies in North Yorkshire

NHS North Yorkshire Talking Therapies

Talking therapies in York and Selby

NHS York and Selby Talking Therapies

Talking therapies in Teesside

Impact on Teesside

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Assessment & Rating Scales

Assessment

Useful questions to screen for depression:

- During the last month, have they often been bothered by feeling down, depressed or hopeless?
- During the last month, have they often been bothered by having little interest or pleasure in doing things?

Factors to consider

- History of depression and coexisting mental health or physical disorders
- History of mood elevation (consider undiagnosed bipolar disorder)
- Personal strengths and resources, including supportive relationships
- Difficulties with previous and current interpersonal relationships
- Current lifestyle (for example, diet, physical activity, sleep)
- Any recent or past experience of stressful or traumatic life events, such as redundancy, divorce, bereavement, trauma
- Living conditions, drug and alcohol use, debt, employment situation, loneliness and social isolation
- Ask directly about suicidal ideation and intent

NICE NG222: Depression in adults: treatment and management

Rating Scales [RCPsych list of rating scales]

- *Beck Depression Inventory (BDI)* – 21 item self-rating scale; helpful for capturing patient experience
- *Hamilton Depression Rating Scale (HAM-D)* – 17 item clinician rated; broad symptom coverage but sleep and physical symptoms can inflate the score (may inflate response to treatment with Mirtazapine)
- *Hospital Anxiety and Depression (HAD) Scale* – 14 item self-rating scale; lacks questions relating to fatigue, sleep, appetite & weight loss which might be caused by medical illness
- *Montgomery-Åsberg Depression Rating Scale (MADRS)* – 10 item clinician rated; focuses on core depressive symptoms and useful for monitoring effect of treatment in clinical trials
- *Patient Health Questionnaire 9 (PHQ-9)* – quick 9 item self-rating scale
- *Quick Inventory of Depressive Symptomatology (QIDS)* – 16-item self-report covering comprehensive symptoms
- *Geriatric Depression Scale (GDS)* – 15-item scale developed for the elderly
- *Hypomania Check List (HCL-16)* – 16-item screening questionnaire for bipolarity

Prescribing in Older Adults

PHARM-0047-v5

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Age Related Factors

Many age-related changes affect medication absorption, distribution, metabolism and elimination. These include:

- Reduced muscle mass
- Reduced hepatic mass
- Reduced renal function
- Reduced gastrointestinal motility
- Reduced total body water
- Increased total body fat
- Increased blood-brain barrier permeability

In addition, response and tolerability of medication can change over time, which all influences prescribing decisions.

Some medicines have dose limits (e.g.es/citalopram) >65yrs.

Toxicity

- Older age is associated with higher rates of accidental and intentional overdose
- There are significant differences in toxicity between medication classes requiring careful consideration with people with history of overdose
- TCAs have high fatality risk, except for Lofepramine
- SNRIs and most antipsychotics are slightly more toxic in overdose than SSRIs and Mirtazapine which are relatively safe options

Key Prescribing Principles

- At all steps, consider non-pharmacological options instead of or in support of drug treatment, e.g. talking therapies
- Consider co-morbid physical health problems
- Avoid medications with adrenergic or cholinergic antagonism due to hypotensive and negative cognitive effects (see Medichec for review of adverse effects)
- Caution with medications with long half-lives or active metabolites due to prolonged effects
- Aim for once daily formulations to reduce tablet burden
- Use lower initial doses and consider slower titration
- Medication trials should be at least 12 weeks at a therapeutic dose due to slower onset of efficacy compared to younger adults

Polypharmacy

The diagnosis of multiple medical conditions increases with age and frequently leads to polypharmacy. Medication prescribed for one condition may have negative effects on another or may interact with another medicine. Polypharmacy increases the risk of adverse effects and admission to acute hospital. Polypharmacy also increases the risk of poor adherence (tablet burden) and administration errors due to confusing regimens

Depression

In need of **ACTIVATION**

GREEN/All Settings: Can be initiated by a GP or in all other care settings. If initiated in TEWV it can be discontinued by primary care without recourse to secondary care.

GREEN+ (DTV&F)

SPECIALIST INITIATION (NYY&S)

Drugs normally recommended or initiated by a specialist. There may be a further restriction for use outlined in the formulary and the provision of additional information may be required for the GP.

General Symptom Profile

Loss of interest
Oversleeping
Overeating
Poor concentration
Indecisive
General slowing

Step 1

Trial of single drug therapy – **4-6 weeks** at treatment dose

SSRI or **Low dose Venlafaxine**

- Sertraline

Initially 50 mg OM
Titrate to at least 100 mg/day

- Venlafaxine

Initially 75 mg/day
Titrate to 150 mg/day

→ Reassess mood using interview & validated rating scale. Check effects of medication and adherence

→ **PARTIAL RESPONSE** Consider increase to maximum dose for further 4-6-week trial if tolerated

Steps 2 & 3

Two further trials of single drug therapy from different groups – **4-6 weeks** at treatment dose

CONSIDER (in any order)

- Alternative SSRI
- Increase Venlafaxine to 150-375 mg/day or switch to Duloxetine if not tolerated
- Vortioxetine (if 2 previous failed or non-tolerated trials)

→ Reassess mood using interview & validated rating scale. Check effects of medication and adherence

→ **PARTIAL RESPONSE** Consider increase to maximum dose for further 4-6-week trial if tolerated

At all steps, consider non-pharmacological options instead of or in addition to drug treatment

Step 4

Associated Guidance

- Psychotropic Medication Monitoring Guide
- Management of QTc Prolongation

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Depression
In need of **SEDATION**

GREEN/All Settings: Can be initiated by a GP or in all other care settings. If initiated in TEWV it can be discontinued by primary care without recourse to secondary care.

GREEN+ (DTV&F)

SPECIALIST INITIATION (NYY&S)

Drugs normally recommended or initiated by a specialist. There may be a further restriction for use outlined in the formulary and the provision of additional information may be required for the GP.

General Symptom Profile

Lack of sleep
Lack of appetite
Agitation/restlessness
Suicidal thoughts
Loss of libido (SSRI not primary choice)

Step 1

Trial of single drug therapy – **4-6 weeks** at treatment dose

Mirtazapine
15-30 mg AT NIGHT
(More sedating at 15 mg)
Not ideal for patients concerned about weight gain

→ Reassess mood using interview & validated rating scale. Check effects of medication and adherence

↓

PARTIAL RESPONSE
Consider increase to maximum dose for further 4-6-week trial if tolerated

←

Steps 2 & 3

Two further trials of single drug therapy from different drug groups – **4-6 weeks** at treatment dose

CONSIDER (in any order)

- SSRI + hypnotic (short term for 2 weeks) **or** + Trazodone 50-100 mg
- Venlafaxine + hypnotic (short term for 2 weeks) **or** + Trazodone 50-100 mg
- Vortioxetine (if 2 previous failed or non-tolerated trials)

→ Reassess mood using interview & validated rating scale. Check effects of medication and adherence

↓

PARTIAL RESPONSE
Consider increase to maximum dose for further 4-6-week trial if tolerated

←

At all steps, consider non-pharmacological options instead of or in addition to drug treatment

Step 4

Associated Guidance
- Psychotropic Medication Monitoring Guide
- Management of QTc Prolongation

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Further Line & Chronic Depression

Step 4 for psychotic depression

GREEN+ (DTV&F)

SPECIALIST INITIATION (NYY&S)

Drugs normally recommended or initiated by a specialist. There may be a further restriction for use outlined in the formulary and the provision of additional information may be required for the GP.

Step 4

Consider in any order – **4-6 weeks** at treatment dose

Alternative MONOTHERAPIES

- Bupropion
- Moclobemide
- Phenelzine
- Tricyclic Antidepressant (TCA)

COMBINATION of Different Antidepressants

- SSRI **or** SNRI + Mirtazapine
- SSRI **or** Mirtazapine + Bupropion

Mood Stabiliser AUGMENTATION of partially effective antidepressants

- Lithium – aim for 0.4-0.8 mmol/L initially
- Lamotrigine

Antipsychotic AUGMENTATION of partially effective antidepressants

- Amisulpride
- Aripiprazole
- Lurasidone (with mixed features)
- Olanzapine
- Quetiapine immediate release (150-300 mg/day)
- Risperidone

Step 5

Consider in any order – **4-6 weeks** at treatment dose

Alternative MONOTHERAPIES

- Agomelatine (if 3 previous failed or non-tolerated trials)

AUGMENTATION of partially effective antidepressants

- SSRI + Buspirone up to 60 mg/day (licensed max. 45 mg/day)
- SSRI **or** Mirtazapine + Reboxetine (2-8 mg/day)

At all steps, consider non-pharmacological options instead of or in addition to drug treatment

Step 6

Associated Guidance

- Psychotropic Medication Monitoring Guide
- Management of QTc Prolongation

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Further Line & Chronic Depression (2)

RED (DTV&F)

SPECIALIST ONLY (NYY&S)

These drugs should only be prescribed in secondary care. Not usually suitable for transfer to primary care

Step 6
Specialist Initiation

Alternative MONOTHERAPIES

- ECT
- Transcranial magnetic stimulation
- Implanted vagus nerve stimulation
- Levothyroxine or Triiodothyronine (Liothyronine)
- Ketamine (IV) – see protocol

Tertiary Referral

Regional Affective Disorders Service (RADS)
Provided by Cumbria, Northumberland, Tyne and Wear (CNTW) NHS trust. Contact: 0191 246 8606
email: RADS@cntw.nhs.uk

At all steps, consider non-pharmacological options instead of or in addition to drug treatment

Psychotic Depression

GREEN+ (DTVF)

SPECIALIST INITIATION (NYY)

Drugs normally recommended or initiated by a specialist. There may be a further restriction for use outlined in the formulary and the provision of additional information may be required for the GP.

Step 4

Consider in any order – **4-6 weeks** at treatment dose

Antipsychotic AUGMENTATION of antidepressants

- Amisulpride
- Aripiprazole
- Olanzapine
- Quetiapine immediate release (150-300 mg/day)
- Risperidone

Back to further Line & Chronic Depression

At all steps, consider non-pharmacological options instead of or in addition to drug treatment

Associated Guidance

- Psychotropic Medication Monitoring Guide
- Management of QTc Prolongation

Evidence Base

Psychotic depression is a severe depression with psychotic features (i.e. delusions and/or hallucinations). It is a largely under researched illness with uncertainty around the most effective drug treatment. Some studies suggest that dysregulation of the hypothalamic pituitary-adrenal axis might be a biologically targeted treatment as abnormalities in the diurnal fluctuation of cortisol have been found and high rates of non-suppression on the dexamethasone suppression test have been observed. Combination of an antidepressant and antipsychotic is preferred for psychotic depression with number needed to treat (NNT) ranging from 5-7 verses individual monotherapies. ECT may be more effective than medications and has a robust evidence as the most effective acute intervention and should be considered early in severe, treatment-resistant, highly psychotic, suicidal, or catatonic presentations. Olanzapine is the best supported antipsychotic option, trials usually in combination with fluoxetine, whereas other antipsychotics are largely extrapolated from treatment-resistant depression or psychosis.

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Evidence Base (1)

Antidepressants

Approximately 20% of people with moderate – severe depression will recover with no treatment at all, 30% will respond to placebo and 50% will respond to antidepressant drug treatment, providing number needed to treat (NNT) of 3 for antidepressant over true no-treatment control and an NNT of 5 for antidepressant over placebo. Response may diminish with second and subsequent medication trials and switching may not be more effective than continuation or augmentation/combination options. Amitriptyline, Mirtazapine and Venlafaxine may be marginally more effective that other antidepressants. However, in a reanalysis focusing on effects on mood, suicidality and anxiety, excluding effects on sleep, appetite, and gastrointestinal dysfunction, Amitriptyline, SSRIs and SNRIs were more effective than Mirtazapine. Agomelatine, Fluoxetine and Escitalopram may be more tolerable than other antidepressants. The options with the best balance of efficacy and tolerability may be Agomelatine, Escitalopram, Sertraline and Vortioxetine. Antidepressant treatment is associated with clinically important adverse effects, including gastrointestinal disturbance, sexual dysfunction, weight change, discontinuation symptoms (particularly with Paroxetine and Venlafaxine), and class-specific risks such as anticholinergic and cardiovascular toxicity with tricyclic antidepressants. Paroxetine and Dosulepin are not approved for use within TEWV. SSRIs may modestly increase suicidal thoughts or behaviours in younger people and are associated with an increased risk of upper gastrointestinal bleeding, particularly when combined with NSAIDs. Long-term continuation therapy substantially reduces relapse risk, especially in recurrent depression, although treatment selection should balance efficacy, tolerability, safety in overdose and individual patient characteristics and preferences.

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Evidence Base (2)

Agomelatine

Agomelatine is licensed for the treatment of depression only (in those > 18 years of age), following a lack of response to at least three alternative antidepressants. It is relatively well tolerated and may be helpful if insomnia is a feature. Liver function must be monitored before treatment and after 3, 6, 12 and 24 weeks of treatment, then periodically or whenever clinically indicated. Monitoring following dose increases should also follow this pattern. Discontinue if serum transaminases exceed 3 times the upper limit of the reference range. Transfer of prescribing to primary care after 6 months. See Primary Care Information sheets: DTVF & NYY

Bupropion

Bupropion is licenced for depression in the US and several European countries (e.g., Germany) but not the UK and is approved for off-label use. Bupropion selectively enhances noradrenergic and dopaminergic neurotransmission through inhibition of noradrenaline and dopamine reuptake. Unlike SSRIs and SNRIs, it has minimal direct serotonergic activity and additionally antagonises nicotinic acetylcholine receptors. Its action is distinct from other antidepressants and may be indicated in patients non-responsive to serotonergic and/or noradrenergic treatments. Doses range from 150mg-400mg however doses >300mg are considered RED and not suitable for transfer to primary care. It's side effects include a "stimulant-like" effect increasing wakefulness and reduced appetite, and low risk of sexual dysfunction but it is potentially proconvulsant and cardiotoxic in overdose. See Primary Care Information sheets: DTVF & NYY

MAOIs

Use of MAOIs may be indicated where there is no response to other antidepressant groups. Unfortunately, there limited direct comparisons between reversable/irreversible MAIOs and against newer antidepressants, however, network meta-analysis suggest irreversible MAOIs may be marginally more effective than reversible but are broadly as effective and tolerable as TCAs and SSRIs. All MAOIs require dietary restriction of tyramine containing foods due to risk of raised blood pressure including hypertensive crisis. Reversible MAOIs may be lower risk than irreversible MAOIs. MAOIs may be helpful treatment resistant cases, particularly atypical depression characterised over-eating, over-sleeping, mood reactivity, and rejection sensitivity. MAOIs should only be initiated by a Consultant Psychiatrist or level 3 NMP with experience in managing MAOIs. See RCPsych MAOI Position Statement

Vortioxetine

Vortioxetine is a "multimodal" agent that enhances release of dopamine, noradrenaline, acetylcholine, and histamine. These actions also modify the release of both glutamate and GABA (gamma amino butyric acid) within various brain circuits. It's potential modes of action seem to be different from the common SSRI and SNRI antidepressants, and it may benefit those patients who complain of cognitive or sexual side effects from those other groups of medications or symptoms of cognitive dysfunction as part of their mood problems.

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Evidence Base (3)

SSRI OR SNRI + Mirtazapine

Generally, antidepressants with different pharmacological profiles are combined. Combining two or even more antidepressants can enhance tolerability, owing to clinical effectiveness of lower doses, e.g. sexual dysfunction due to SSRI treatment may be reduced using lower dosages within combined treatment. Pharmacokinetic interactions may increase the risk for severe adverse events, e.g. serotonin syndrome. There is reasonable literature support for their use, particularly antagonists of presynaptic α2-autoreceptors (namely Mirtazapine and to a lesser extent Mianserin and Trazodone) though there are conflicting studies suggesting no benefit over monotherapy. Addition of Mirtazapine may be most beneficial where insomnia, poor appetite or weight loss are prominent and where sedation and weight gain are acceptable or desired.

SSRI OR Mirtazapine + Bupropion

Evidence from two RCTs support Bupropion combination with a variety of other antidepressants, mainly SSRIs, however meta-analyses has not demonstrated consistent superiority over antidepressant monotherapy. Response may be seen in around 30% of patients; however, comparative studies suggest similar efficacy with Bupropion monotherapy and superiority of alterative augmentation options e.g. Aripiprazole.

SSRI + Buspirone

Buspirone, a partial agonist at the postsynaptic 5-hydroxytryptamine$_{1A}$ (5-HT$_{1A}$) receptor may enhance the activity of SSRIs. The evidence for buspirone augmentation is mainly based on two controlled studies and mainly points towards an initial acceleration of response. May be beneficial for anxious or agitated presentations.

SSRI OR Mirtazapine + Reboxetine

The evidence base for this combination is limited to older open-label studies and case series with small sample sizes. These studies suggest Reboxetine may be effective and well tolerated, however the data is superior for alternative augmentation strategies

Aripiprazole

Aripiprazole may be considered a first line antipsychotic augmentation due to robust evidence base and favourable tolerability profile. Meta-analyses demonstrate improved response compared with placebo/antidepressant therapy alone and Aripiprazole performs well against other adjunctive antipsychotics on acceptability, with common side effects being akathisia, insomnia/somnolence and fatigue. Partial-agonist activity at the D2/D3 receptors, in addition to partial-agonist activity at the serotonin 1A (5-HT1A) receptor appear to contribute to efficacy. Optimal dose appears to be around of 5mg daily with higher doses failing to provide better efficacy but greater side effect burden.

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Evidence Base (4)

Olanzapine

Olanzapine has supportive evidence (although less robust than Quetiapine or Aripiprazole) for improved depression symptomatology and higher rates of remission or response in the treatment of people with no or limited response to initial antidepressant treatment but clinical implications are uncertain. High-quality studies reporting efficacy of Olanzapine augmentation are limited to SSRIs (mainly Fluoxetine) and largely in the context of treatment resistance, with little benefit of augmentation of TCAs or SNRIs and many are hampered by manufacturer sponsorship. Effective doses range from 6-12 mg/day with limited benefit of higher doses. Olanzapine use is significantly associated with metabolic adverse effects contributing to treatment discontinuation therefore requires risk vs benefit assessment given the low-quality evidence base. Use is off-label and requires discussing with the patient and documenting as such.

Quetiapine

Quetiapine immediate-release (IR) recommended off-label due to cost implications of MR formulations. The MR formulation is licenced for augmentation of antidepressant treatment at doses 150–300mg/ day and both IR and MR can be given as one daily dose at bedtime. Double-blind, placebo-controlled studies showed significant superiority for Quetiapine add on vs. placebo in the acute treatment of unipolar depression, however higher drop-outs due to tolerability, namely sedation, daytime somnolence, weight gain and metabolic effects. It may be particularly helpful when insomnia, anxiety or agitation are clinical features. There is good evidence for the efficacy of Quetiapine monotherapy in acute and long-term treatment of unipolar depression although no license has been granted in the UK (off-label use).

Risperidone

Risperidone has supportive evidence from uncontrolled, lower quality or short-term studies than other augmentation options. Several studies were open-label design, and most were short-term (<6weeks) which limits robust conclusion. These demonstrate improved depression symptomatology and higher rates of response or remission following limited response to initial antidepressant treatment, but clinical implications are uncertain. This small effect has been demonstrated in studies augmenting with both SSRIs and SNRIs with similar efficacy. Doses range from 250microgram to 3mg/day in studies with doses adjusted according to response. Risperidone demonstrated a favourable adverse effect profile (compared to other atypical antipsychotics) in one meta-analysis though raised concerns about study design though post-hoc analysis.
Use is off-label and requires discussing with the patient and documenting as such.

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Evidence Base (5)

Lurasidone

An estimated 25-45% people with major depression present with manic symptoms below the threshold for hypomania (mixed features). The evidence base for Lurasidone in unipolar depression is limited to one placebo-controlled RCT specifically in people with depression and mixed features, which limits extrapolation to depression in the absence of mixed features. This study demonstrates significantly improved depressive symptoms and overall illness severity with moderate to high effect size alongside significant improvement in manic symptoms at doses ranging from 20–60 mg/day. A transdiagnostic systematic review suggests Lurasidone may exhibit efficacy on depressive symptomatology across a range of psychiatric diagnoses.

Lamotrigine

Lamotrigine's primary action is to modulate voltage-gated sodium channels. Evidence suggests that it decreases glutamate transmission, directly reduces calcium influx, mildly blocks transmitter reuptake, and alters intracellular mechanisms of resting transmitter release. Studies have shown evidence of efficacy for lamotrigine in bipolar depression however; in unipolar depression the evidence is mixed. There is very low-quality evidence from 8 RCTs (N=599) demonstrating a clinically important and statistically significant benefit of augmenting antidepressant treatment with lamotrigine, relative to monotherapy antidepressant or placebo augmentation, on depression symptomatology but little effect on response or remission rates. Lamotrigine is generally well tolerated. It requires slow dose titration due to rare skin reactions which may delay reaching therapeutic doses for 6-8 weeks. Target doses range from 150-250mg/day.

Amisulpride

Use in dysthymia, and to a lesser extent depression, has some good evidence thought notably weaker than other augmentation options. At low doses of 50-150mg it's mechanism may be via selective D2/D3 auto-receptor antagonism enhancing dopamine transmission. Higher doses may help more in cases of psychosis with depression.

Lithium

Lithium can be useful in treatment refractory presentations with robust evidence of response, but weaker evidence for symptom remission. A suggested practical criteria for starting lithium is two episodes of depression in five years. Levels can be as low as 0.4mmol/l to be effective as an augmentation agent, but if there is no response at these levels then further increases should be trialled up to levels on 0.8mmol/l if tolerated. Physical health and plasma monitoring is required. Maintaining levels <0.8mmol/l and using a single nightly dose reduces risk of renal impairment. There is evidence in unipolar depression that augmentation with Lithium reduces suicidality. Also, augmentation of TCAs with Lithium may be more effective than addition of Lithium to SSRIs. Urgent action is required to manage toxicity (levels >1mmol/l). See Learning from Errors No 12 and MSS 2; Shared Care Protocols: DTVF & NYY and additional Information to support the specialist role in shared care.

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Evidence Base (6)

Levothyroxine (T4) / Liothyronine (T3)

Thyroid disorders and depression commonly coexist and share symptoms such as fatigue and low mood, which may contribute to poor antidepressant response. Although TSH is the main marker of thyroid function, the upper limit of the reference range remains debated. Many symptomatic patients with “high-normal” TSH levels may have mild hypothyroidism. Evidence for thyroid hormone augmentation in depression is mixed. Most studies are small and focus on tricyclic antidepressants, with limited evidence for newer antidepressants. However, liothyronine (T3) may accelerate and enhance antidepressant response in treatment-resistant depression, while supraphysiological levothyroxine (T4) has shown benefit in refractory unipolar and bipolar depression. Levothyroxine is inexpensive and widely available, whereas liothyronine is costlier and less consistently available but has a larger evidence base. Typical starting doses are 50-100 µg/day for T4 and 20-50 µg/day for T3, with monitoring of symptoms, adverse effects, and TSH, aiming for a level below 2 µIU/mL. Both T3 and T4 are generally well tolerated. Potential adverse effects include tachycardia, atrial fibrillation, hypertension, reduced bone density, osteoporosis, and high-output cardiac failure. Patients should be monitored regularly, and those at increased risk of osteoporosis, such as post-menopausal women, should be considered for bone-protective measures.

Ketamine

Ketamine is commonly used as a sedative and analgesic in emergency medicine, as well as a general anaesthetic. It is a novel treatment for depression with a mechanism of action via glutaminergic antagonism which is distinct from other treatments. It has a substantial evidence base demonstrating efficacy in treatment-resistant depression and reduction in suicidality and has RCPsych support within specialist settings with appropriate oversight and monitoring.

There are no licenced formulations of ketamine for depression in the UK. An analogue of ketamine, esketamine, has been licensed as an intranasal formulation, but is not recommended by NICE (TA854) due to concerns around cost-effectiveness. Ketamine is non-formulary and requires single patient application review by a panel.

Ketamine is given by IV infusion on a weekly or twice-weekly regimen for a maximum of 6 weeks for the acute phase of treatment. Then this will continue at an extended time frame for maintenance., e.g., weekly, fortnightly etc. based on clinical needs. Response rates in controlled trials have ranged from 25% to 85% at 24 hours post infusion and from 14% to 70% at 72 hours post infusion. The mean time to relapse after the acute phase was 19 days and optimal duration of long-term treatment remains uncertain. Side effects include dissociation, blood pressure changes, tachycardia, abdominal discomfort, abnormal sensations, weakness, fatigue and headaches. Concerns remain around long-term effects on urinary tract toxicity and the wider risks of tolerance, dependence and misuse; however, the structured protocols mitigate these risks.

Switching Medications (1)

From \ To	Agomelatine[1]	Bupropion[2]	Clomipramine	Fluoxetine[3]	MAOIs	Moclobemide	Mirtazapine	Reboxetine[4]	Other SSRIs[5]	SNRIs	TCAs (except Clomipramine)	Trazodone	Vortioxetine[6]
Agomelatine[1]		Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously
Bupropion[2]	Cross-taper cautiously		Cross-taper cautiously	Cross-taper cautiously	Withdraw & wait for 2 weeks	Withdraw then start with low dose	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously start with low dose	Cross-taper cautiously	Cross-taper cautiously
Clomipramine	Cross-taper cautiously	Cross-taper cautiously		Withdraw then start Fluoxetine at 10mg/day	Withdraw & wait for 3 weeks	Withdraw & wait 1 week	Cross-taper cautiously	Cross-taper cautiously	Withdraw then start with low dose	Withdraw then start with low dose	Cross-taper cautiously	Cross-taper cautiously	Withdraw then start with low dose
Fluoxetine[3]	Cross-taper cautiously	Withdraw & wait 4-7 days then start low dose	Withdraw & wait for 2 weeks then start low dose		Withdraw & wait 5-6 weeks	Withdraw & wait 5-6 weeks	Cross-taper cautiously	Cross-taper cautiously	Withdraw & wait 4-7 days then start low dose	Withdraw & wait 4-7 days then start low dose	Withdraw & wait 4-7 days then start low dose	Cross-taper cautiously	Withdraw & wait 4-7 days then start low dose
MAOIs	Cross-taper cautiously	Withdraw & wait for 2 weeks	Withdraw & wait for 3 weeks	Withdraw & wait for 2 weeks	Withdraw & wait for 2 weeks	Withdraw & wait for 2 weeks	Withdraw & wait for 2 weeks	Withdraw & wait for 2 weeks	Withdraw & wait for 2 weeks	Withdraw & wait for 2 weeks	Withdraw & wait for 2 weeks[9]	Withdraw & wait for 2 weeks	Withdraw & wait for 2 weeks
Moclobemide	Withdraw & wait 24 hours	Withdraw & wait 24 hours	Withdraw & wait 24 hours	Withdraw & wait 24 hours	Withdraw & wait 24 hours		Withdraw & wait 24 hours	Withdraw & wait 24 hours	Withdraw & wait 24 hours	Withdraw & wait 24 hours	Withdraw & wait 24 hours	Withdraw & wait 24 hours	Withdraw & wait 24 hours
Mirtazapine	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Withdraw & wait for 2 weeks	Withdraw & wait 1 week		Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously

Note: Adapted from The Maudsley Prescribing Guidelines 15th Edition. Advice given in this table is partly derived manufacturers' information and partly theoretical. Caution is required in every instance. See Notes

Switching Medications – Continued

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Switching Medications (2)

From \ To	Agomelatine[1]	Bupropion[2]	Clomipramine	Fluoxetine[3]	MAOIs	Moclobemide	Mirtazapine	Reboxetine[4]	Other SSRIs[5]	SNRIs	TCAs (except Clomipramine)	Trazodone	Vortioxetine[6]
Reboxetine[4]	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Withdraw & wait 1 week	Withdraw & wait 1 week	Cross-taper cautiously		Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously
Other SSRIs[5]	Cross-taper cautiously	Cross-taper cautiously	Withdraw then start with low dose	Direct switch possible[7]	Withdraw & wait 1 week	Withdraw & wait 1 week	Cross-taper cautiously	Cross-taper cautiously	Direct switch possible[8]	Direct switch possible[8]	Cross-taper cautiously start with low dose	Cross-taper cautiously starting with low dose	Direct switch possible[8]
SNRIs	Cross-taper cautiously	Cross-taper cautiously	Withdraw then start with low dose	Direct switch possible[7]	Withdraw & wait 1 week	Withdraw & wait 1 week	Cross-taper cautiously	Cross-taper cautiously	Direct switch possible[8]	Direct switch possible[8]	Cross-taper cautiously start with low dose	Cross-taper cautiously	Direct switch possible[8]
TCAs (except Clomipramine)	Cross-taper cautiously	Halve dose and add bupropion then slow withdrawal	Direct switch possible[8]	Halve dose and add fluoxetine then slow withdrawal	Withdraw & wait for 2 weeks[9]	Withdraw & wait 1 week	Cross-taper cautiously	Cross-taper cautiously	Halve dose and add SSRI then slow withdrawal	Cross-taper cautiously start with low dose	Direct switch possible[8]	Halve dose and add trazodone then slow withdrawal	Halve dose and add vortioxetine then slow withdrawal
Trazodone	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously start with low dose	Cross-taper cautiously	Withdraw & wait 1 week	Withdraw & wait 1 week	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously start with low dose		Cross-taper cautiously
Vortioxetine[6]	Cross-taper cautiously	Cross-taper cautiously	Withdraw then start with low dose	Direct switch possible[7]	Withdraw & wait 3 weeks	Withdraw & wait 1 week	Cross-taper cautiously	Cross-taper cautiously	Direct switch possible[8]	Direct switch possible[8]	Cross-taper cautiously start with low dose	Cross-taper cautiously	

Note: Adapted from The Maudsley Prescribing Guidelines 15th Edition. Advice given in this table is partly derived manufacturers' information and partly theoretical. Caution is required in every instance. See Notes

Switching Medications – Continued

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Switching Medications (notes)

Adapted from The Maudsley Prescribing Guidelines 15th Edition. Advice given in the table is partly derived manufacturers' information and partly theoretical. Caution is required in every instance.

[1] Agomelatine has no effect on monoamine uptake and no affinity for α, β adrenergic, histaminergic, cholinergic, dopaminergic and benzodiazepine receptors. The potential for interactions between agomelatine and other antidepressants is low and it is not expected to mitigate discontinuation reactions of other antidepressants. Some crossover with other antidepressants might be cautiously attempted when switching from agomelatine

[2] Bupropion is a CYP2D6 inhibitor and particular caution is required when cross-tapering with drugs metabolised by this enzyme

[3] Beware: interactions with fluoxetine may still occur for 5 weeks after stopping fluoxetine because of its metabolite's long half- life

[4] Switching to reboxetine as antidepressant monotherapy is no longer recommended

[5] Citalopram, escitalopram and sertraline

[6] Limited experience with vortioxetine and extra caution is required. Take particular care when switching to or from bupropion and other CYP2D6 inhibitors such as fluoxetine and paroxetine (not approved in TEWV)

[7] Caution when directly switching to fluoxetine. Some overlap (a few days) may be advisable to allow fluoxetine plasma concentration to build up before stopping the first antidepressant. Switching from vortioxetine is a probable exception to this, given its long half- life

[8] Direct switch from between SSRIs and SNRIs or Vortioxetine are possible. If on higher doses i.e. close to BNF maximum, aim to down titrate to a standard dose before switching to the next treatment at a standard does e.g. Sertraline 100mg to Duloxetine 60mg

[9] Wait 3 weeks in the case of imipramine.

Further Information

- SPS Switching Guide

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Deprescribing (1)

When to Stop

Depression is common, affecting around 5.7% of adult populations, and medications are an effective treatment strategy for hastening recovery, reducing symptoms and minimising relapse. Continuing medication after the resolution of acute symptoms reduces the risk of relapse by around 50% and following first episode treatment should be continued for at least 6-9 months. In recurrent illness, treatment should be continue for 1-2 years or consider long-term use (5 of more episodes). Relapse is more likely following discontinuation compared to continuing antidepressants. However, most studies used medication taper over 4 weeks which may obscure the true relapse rates through medication withdrawal effects.

De-prescribing should be a collaborative decision following a structured process to reduce the risk of relapse and discontinuation effects. If there are multiple medications prescribed, the order of de-prescribing should be led by clinical need and patient preference e.g. if Mirtazapine and Venlafaxine are prescribed and weight gain is a problem then stopping Mirtazapine would take priority.

How to Stop

The flowchart can help guide decisions around discontinuation. Abrupt stopping of anti-depressants can increase the risk of relapse. The faster the discontinuation the greater the risk of relapse and withdrawal symptoms. Linear reductions of dose e.g. Sertraline 150mg, 100mg, 50mg, do not equate to linear reductions of pharmacological effect and tapering plans should be flexible and consider progressive reductions by 25-50% of the previous dose.

All antidepressants have a risk of discontinuation effects ranging from anxiety symptoms to flu-like symptoms and ‘electric shock’ effects. Discontinuation effects are not harmful but can be very uncomfortable. If discontinuation effects occur a slower taper should be instigated. This is less likely to be required with Fluoxetine because of its long half-life. See Withdrawal Risk Assessment Tool.

Next Step

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Deprescribing (2)

Review

STEP 1: SHOULD I DEPRESCRIBE? – Deprescribing triggers
Risk > benefit, no ongoing benefit, resolution of stressors, alternate coping strategies developed, completion of treatment course, uncertainty about the efficacy for relapse prevention, preference for alternative treatments, adverse effects, tolerability, drug interaction, drug-disease interaction, high drug burden index (DBI), poor adherence

1a. Is there a documented indication or symptoms supporting continued use?
Inappropriate indication for continued use:
No current depression symptoms >6 months
Consult/review with mental health specialist if applicable.
Do not deprescribe if:
Recurrent or severe depression or severe OCD or GAD.
If there remains significant risk of relapse, particularly if there are residual depressive symptoms.
Discuss with mental health specialist if applicable.

1b. Are there adverse effects?
Consider potential adverse effects:
Agitation, anxiety, blurred vision, confusion, constipation, delirium, diarrhoea, dizziness, drowsiness, dry eyes, dry mouth, falls, headaches, hyponatraemia, hypotension, insomnia, myalgia, nausea, palpitations, QT prolongation, rash, rhinitis, sexual dysfunction, sweating, tachycardia, tremor, urinary retention, weakness, weight gain

1c. Is this medication likely to cause more harm than benefit?
Consider the risks of harm and benefits of continued use.

Next Step

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Deprescribing (3)

Discuss

STEP 2: Does the patient/carer agree with the recommendation to deprescribe?
Over 90% of people would be willing to stop their medicines if recommended by their physician. Following provision of information (see patient information leaflets from RCPsych and Choice and Medication **Nb.** For TEWV employees or patient/carer access only), discussion and shared decision making, the patient or carer has communicated that they would like to proceed with or decline the deprescribing recommendation.
Consider the possible 'nocebo' effect, involving expectations for poor reactions to medication discontinuation.

Reduce

STEP 3: HOW DO I DEPRESCRIBE?
Establish a supportive and trusting relationship with the patient to engage in complex/ sensitive discussions.
Accompany weaning with commencement of relevant non-pharmacological support.
Reduce dose slowly by 25-50% of the daily dose every 1-4 weeks.
In patients prescribed high doses for longer periods a more gradual reduction plan may be more appropriate. Certain antidepressants with a higher risk of discontinuation effects require a more cautious reduction (see withdrawal risk tool).
Consider weaning faster if deprescribing reason due to adverse effects.
Organise prescriber follow up appointment to monitor progress (frequency determined by rate of weaning)
Provide advice on self-monitoring and what to do if symptoms re-occur.

Next Step

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Deprescribing (4)

Reduce

3a) How to wean.

Initiation: Reduce dose slowly by 25-50% of the daily dose every 1-4 weeks.

Adjust according to response.

If no discontinuation effects occur, continue to wean, and stop. Some patients may be able to tolerate faster tapers than others. It is important to work collaboratively and reduce medication at the patient's preferred pace. See Example Deprescribing Plans. If withdrawing Pramipexole, see Pramipexole Deprescribing. Ensure the plan is documented and shared with the patient.

Consider slower weaning (e.g. 12.5%) when reducing to the final lowest dose, as this is where the majority of withdrawal effects present.

Liquid formulations may be required for smaller dose tapering.

Avoid alternate day dosing towards the end, unless using Fluoxetine, as this can cause withdrawal effects. Switching to Fluoxetine can aid with weaning if dosage forms are limited.

Adjust according to recurrent symptoms

If recurrent/withdrawal symptoms occur, restart medication at the last effective/tolerable dose.

Recommence weaning after 6-12 weeks with smaller dose reductions (e.g. 5-12.5% of daily dose each month) then stop.

Next Step

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Deprescribing (5)

Monitor

STEP 4: MONITORING

1-3 Days
Discontinuation symptoms usually occur shortly after dose reductions though can be delayed in if the medication has a long half-life

>7 Days
Re-emergence of depression or anxiety typically takes longer – weeks or months

Common withdrawal symptoms, often called ‘discontinuation syndrome’ (e.g. anxiety, gastrointestinal effects, insomnia, irritability, and sweating) are usually mild, highly variable and can last up to 6-8 weeks (longer in some cases). See Withdrawal Effects.
If severe symptoms (e.g. impaired concentration, motor restlessness, tremor, muscle pain, muscle twitching, tachycardia, hypertension, sweating, generalised tonic-clonic seizures, perceptual disturbance, nausea, bloating, anorexia, severe anxiety, or severe insomnia) occur, restart at the previous lowest effective dose
There may be a delay before withdrawal symptoms present for patients on higher doses of Fluoxetine because of the longer half-life

Next Step

Withdrawal Risk Tool | **Withdrawal Effects** | **Example Deprescribing Plans**

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Deprescribing (6)

Alternative Management

NON-PHARMACOLOGICAL SUPPORT

Medication is not first-line for many mental health conditions and there are multiple evidence-based non-pharmacological interventions available. See Psychological Interventions. Relapse is less likely when deprescribing is used in conjunction with non-pharmacological support.

Consider:

- Cognitive behavioural therapy
- Guided self-help
- Interpersonal therapy
- Physical activity
- Problem-solving techniques
- Psychodynamic psychotherapy
- Social prescribing
- Supportive counselling

Withdrawal Risk Tool | Withdrawal Effects | Example Deprescribing Plans

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Withdrawal Risk Tool

Duration	Weighting
Short term (1–6 months)	0 points
Intermediate term (6–12 months)	1 point
Long term (1–3 years)	2 points
Very long-term use (> 3 years)	3 points
Antidepressant type	
Lowest risk (Agomelatine)	0 points
Low risk (Vortioxetine,, Milnacipran, Trimipramine, Dosulepin)	1 point
Moderate risk (Citalopram, Escitalopram, Sertraline, Fluoxetine; Amitriptyline, Nortriptyline, Clomipramine, Lofepramine)	2 points
High risk (Duloxetine, Venlafaxine; Paroxetine; Phenelzine, Moclobemide; Mirtazapine)	4 points
Dosage	
Minimum therapeutic dosage or lower	0 points
Greater than the minimum therapeutic dosage	1 point
Past experience of withdrawal symptoms	
Stopped antidepressant in past with no withdrawal symptoms/unknown	0 points
Mild to moderate withdrawal symptoms	1 point
Severe withdrawal symptoms	2 points
Very severe withdrawal symptoms	3 points

Low risk = 0 points. Medium risk = 1–4 points. High risk = 5–8 points. Very high risk = >9 points

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Horowitz M.A, et al. Estimating Risk of Antidepressant Withdrawal from a Review of Published Data. CNS Drugs. 2023 Feb;37(2):143-157
Horowitz, M.A, & Taylor, D. M. (2024). The Maudsley Deprescribing Guidelines: Antidepressants, Benzodiazepines, Gabapentinoids and Z-drugs

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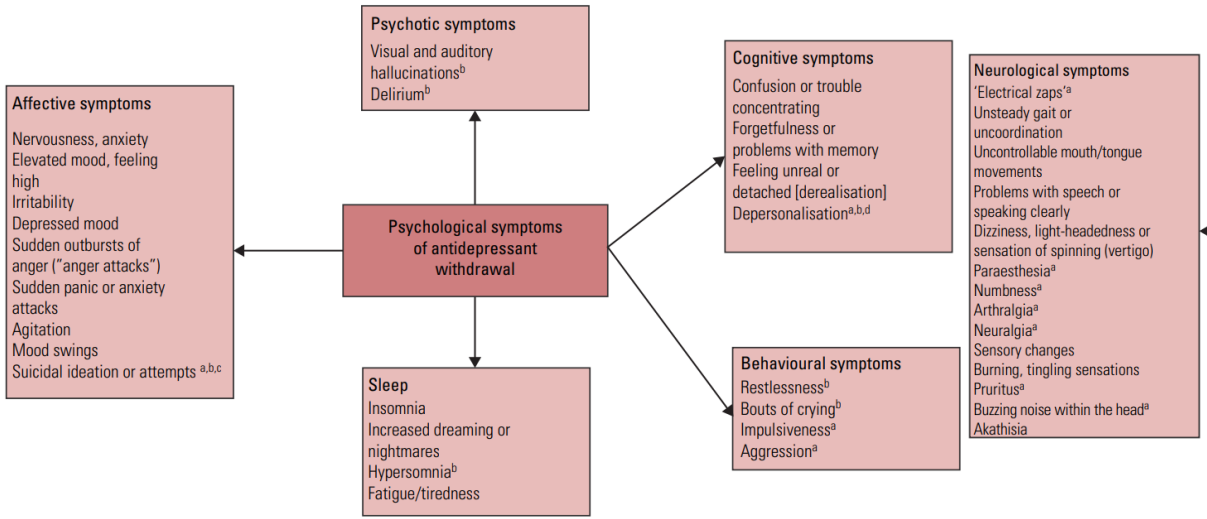
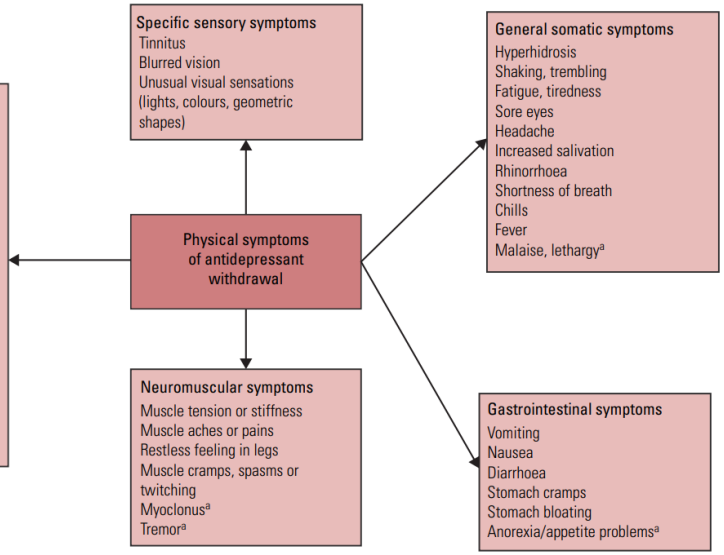
Withdrawal Effects

Psychological Symptoms



Physical Symptoms



Images extracted from Horowitz MA, Taylor D. Distinguishing relapse from antidepressant withdrawal: clinical practice and antidepressant discontinuation studies. BJPsych Advances. 2022;28(5):297-311

Most of the listed symptoms are derived from the Discontinuation-Emergent Signs and Symptoms checklist (Rosenbaum 1998).
Symptoms derived from other sources are referenced individually:
Figure 1: Psychological symptoms: a, Fava et al (2015); b, Cosci & Chouinard (2020); c, Valuck et al (2009); d, Rusconi et al (2009).
Figure 2: Physical symptoms: a, Cosci & Chouinard (2020).

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Example De-prescribing Plans

Key Deprescribing Principle
Reductions should be guided by the patient's experience and adjusted to optimise tolerability

Example Faster De-prescribing Plan

Reduction from e.g. Citalopram 20mg after 6 months treatment:
Step 1: Reduce to Citalopram 10mg daily for 2 weeks and reassess,
Step 2: Reduce to Citalopram 5mg daily for 2 weeks and reassess,
Step 3: Reduce to Citalopram 2.5mg daily for 2 weeks and stop.
Follow up with clinician e.g. fortnightly after discontinuation

Example Slower De-prescribing Plan

Reduction from e.g. Sertraline 200mg after 12 months treatment
Step 1: Reduce to Sertraline 150mg daily for 4 weeks and reassess,
Step 2: Reduce to Sertraline 100mg daily for 4 weeks and reassess,
Step 3: Reduce Sertraline 75mg daily for 4 weeks and reassess,
Step 4: Reduce Sertraline 50mg daily for 4 weeks and reassess,
Step 5: Reduce to Sertraline 25mg daily for 4 weeks and reassess,
Step 6: Reduce to Sertraline 12.5mg daily for 4 weeks and stop
Follow up with clinician e.g. fortnightly after discontinuation

Example Hyperbolic De-prescribing Plan

	Citalopram (mg/day)	Escitalopram (mg/day)	Fluvoxamine (mg/day)	Paroxetine (mg/day)	Sertraline (mg/day)	Duloxetine (mg/day)	Venlafaxine (mg/day)
Step 1	20·0	10·00	50·0	20·0	50·00	60·0	75·0
Step 2	10·0	5·00	30·0	10·0	25·00	30·0	37·5
Step 3	6·0	3·00	20·0	7·0	15·00	15·0	20·0
Step 4	4·0	2·00	15·0	5·0	10·00	10·0	12·0
Step 5	3·0	1·50	10·0	3·0	7·50	6·0	7·0
Step 6	2·0	1·00	5·0	2·0	5·00	4·0	5·0
Step 7	1·0	0·50	2·5	1·0	2·50	2·0	3·0
Step 8	0·5	0·25	0·0	0·5	1·25	1·0	2·0
Step 9	0·0	0·00	..	0·0	0·00	0·0	1·0
Step 10	..	..	..	..	..	..	0·0

Hyperbolic reductions are calculated based on a desired 10% reduction in serotonin transporter occupancy per step, following the Michaelis–Menten equation: Dose = (Occupancy / B_{max}) × (ED_{50}/ (1-Occupancy / B_{max}), where B_{max} is the maximal occupancy possible, ED_{50} is the dose with 50% occupancy, and both are determined per drug on the basis of PET data (appendix pp 14). Depending on occurrence and tolerability of antidepressant withdrawal symptoms, which might still be occurring when following these steps, the interval between steps (or dosages) can be adjusted via shared decision making by the patient and physician. This Taskforce does not consider prolonged use of any dosage of these discontinuation steps without further attempts of discontinuation as being rational pharmacotherapy. SNRI=serotonin–norepinephrine reuptake inhibitor.

Table: Steps in dosing to discontinue SSRIs and SNRIs in case of one or more risk factors for acute withdrawal syndrome

Extract from Ruhe, H.G., et al. (2019). Tapering of SSRI treatment to mitigate withdrawal symptoms. The lancet. Psychiatry, 6(7), 561–562.
Note: hyperbolic tapering is currently theoretical, however there is an active RCT testing this approach

Further Information

- SPS deprescribing antidepressants
- RCPsyc Stopping Antidepressants patient information leaflet

Choice and Medication handy fact sheets for:

- Stopping antidepressants
- Specific leaflets for several SSRIs

Nb. For TEWV employees or patient/carer access only

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Appendix 1: References (1)

Antidepressants

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SSRI OR SNRI + Mirtazapine

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SSRI OR Mirtazapine + Reboxetine

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Definitions

Combination
A combination of two or more treatments, each of which represents an antidepressant alone, i.e. it adds an extra effect without altering the action of the first drug

Augmentation
Augmentation means adding another drug that by itself is not an antidepressant, but that may improve the efficacy of the original antidepressant.

Partial Response
Failure to respond completely to a course of single drug therapy

Off-label
Prescribing a licensed medication for a condition outside of its product licence

Unlicensed
Prescribing a medicine that does not have a UK marketing licence

CBT
Cognitive behavioural therapy (CBT) is a type of psychotherapy that helps people change their thoughts and behaviours to improve their feelings

Mixed Features
Presence of 2-3 manic symptoms, on most days for at least 2 weeks: elevated or expansive mood, inflated self-esteem or grandiosity, more talkative than usual or pressure to keep talking, flight of ideas or racing thoughts, increased energy, increased or excessive involvement in activities with a high potential for negative consequences, and decreased need for sleep

NMP Non-medical prescriber
SAF Single application form
ECT Electro convulsant therapy
MAOI Monoamine oxidase inhibitor
OTC Over-the-counter medications
SSRI Selective serotonin reuptake inhibitor
SNRI Serotonin and noradrenaline reuptake inhibitor
TCA Tricyclic antidepressant

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Document Changes

Ver.	Date of change	Details of change
5.0	23/9/26	• New format and full refresh • Evidence base updated • Inclusion of slides on assessment, rating scales, toxicity, psychological support, and deprescribing • Bupropion moved to step 4 in line with formulary approval for off-label use • Reboxetine moved to step 5 in line with lower evidence for efficacy • Lurasidone added for unipolar depression with mixed features in line with formulary approval • Pramipexole added for treatment resistant depression • Ketamine IV added for treatment resistant depression N.b. This policy document was drafted by NHS staff with technical, administrative, and editorial assistance from Microsoft Copilot, with all final content thoroughly reviewed and verified by the authors.

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