**Depression: Medication Treatment & Deprescribing Pathway for Adults**

The aim of this pathway is to encourage safe and efficient prescribing by advising the best evidence based pharmacological treatments for unipolar depression.

**Patients aged over 65 years:** Any doses stated refer to adult dosing and the prescriber should consult the BNF for advice on doses for elderly patient groups.

**Key prescribing guidelines**

* At all steps, consider non-pharmacological options instead of or in support of drug treatment, e.g. talking therapies
* Request a full list of medical problems and medication from the GP
* Consider causative underlying physical health problems
* Consider monotherapy first
* Before initiating treatment, explain the risk of discontinuation symptoms and how these can be minimised; explain the potential for increased suicidality during early weeks of treatment. Refer to the [Medication Safety Bulletin: “Toxicity of Psychotropic Medication in Overdose”](https://intranet.tewv.nhs.uk/download.cfm?ver=13262) to guide decisions on medication choice
* Medication trials should be at least 4 weeks at the maximum tolerable dose
* Combination or augmentation may be more effective when there is partial response
* Antidepressants used for alternative indications at low doses (e.g. trazodone to aid sleep) should be taken into consideration but are not considered combination treatment
* Any benzodiazepine or hypnotic prescription should be used with caution and short term use only (maximum 2 weeks)
* Deprescribing and Swapping & Stopping advice is provided [here](#_Consultation_and_Prescribing)

**Definitions**

* Combination = 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 = adding another drug that by itself is not an antidepressant, but 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 medicine for a condition outside its marketing authorisation
* Unlicensed = prescribing a medicine that does not have a UK marketing authorisation

**Off-label and Unlicensed Medicines**

In later steps, the choices are often off-label; this is highlighted where necessary. Before prescribing off-label or unlicensed medicines the following conditions must be met:

* The medicine is better suited to the patient’s needs than an appropriately licensed alternative
* There is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy
* The reasons why medicines are not licensed for their proposed use should be explained to the patient, or parent/carer
* A clear and accurate record of medicines and the rationale for use should be documented on the EPR (unless the medication is included in TEWV off-label permissions) as part of the Medication Treatment Plan
* Off-label and unlicensed medications monitoring and prescribing arrangements are likely to remain in secondary care unless transfer has been agreed

**Depression With Personality Disorder**

Manage as per depressive episode including psychological and pharmacological treatments. Consider diagnosis of co-morbid Depression

**(N) = recommended by NICE guidelines**

**\* = should only be initiated by a Consultant Psychiatrist or Level 3 NMP with appropriate competency**

**In need of ACTIVATION**

* Loss of interest
* Oversleeping
* Overeating
* Poor concentration
* Indecisive
* General slowing

**In need of SEDATION**

* Lack of sleep
* Lack of appetite
* Agitation/restlessness
* Suicidal thoughts
* Loss of libido\*

\* SSRI not primary choice

**SSRI (N) or low dose Venlafaxine**

* Sertraline initially 50mg, titrated to at least 100mg/day
* Venlafaxine up to 150mg/day

**Mirtazapine**

30mg AT NIGHT

(more sedating at 15mg)

Not ideal for patients concerned about weight gain

Reassess mood using interview and a validated rating scale

Check effects of medication and adherence

Reassess mood using interview and a validated rating scale

Check effects of medication and adherence

PARTIAL RESPONSE

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

**General**

**Symptom**

**Profile**

**STEP 1**

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

**STEPS 2 & 3**

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

**CONSIDER (in any order)**

* + A different SSRI if the first is not tolerated **(N)**
* Increase venlafaxine to 150-375 mg/day or switch to duloxetine if not tolerated **(N)**
* [Vortioxetine](#Vortioxetine) **(N)** (if 2 previous failed or non-tolerated trials)

**CONSIDER (in any order)**

* Venlafaxine + hypnotic

(short term for sleep 2 weeks) **or** + trazodone 50-100 mg

* SSRI + hypnotic

(short term for sleep 2 weeks) **or** + trazodone 50-100 mg

* [Vortioxetine](#Vortioxetine) **(N)** (if 2 previous failed or non-tolerated trials)

Reassess mood using interview and a validated rating scale

Check effects of medication and adherence

Reassess mood using interview and a validated rating scale

Check effects of medication and adherence

PARTIAL RESPONSE

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

**NO RECOVERY**

**NO RECOVERY**

**NO RECOVERY**

Consider seeking advice from a Specialist

**PARTIAL RECOVERY**

Add Psychological Therapy

if not already tried

**STEP 5**

Specialist Initiation/Recommendation

Consider in any order;4-6 weeks at treatment dose

**NO RECOVERY**

[**AUGMENTATION**](#Augmentation) **of partially effective antidepressants**

* [SSRI + buspirone](#SSRIplusBuspirone) up to 60 mg/day (licensed max. 45 mg/day)
* [Bupropion](#Bupropion)\* (off-label)

**STEP 6**

Secondary Care Only

**NO RECOVERY**

* ECT
* Transcranial magnetic stimulation
* Implanted vagus nerve stimulation
* [Levothyroxine or Triiodothyronine (Liothyronine)](#Triiodothyronine) (off-label) **(N)**

**STEP 4**

Specialist Initiation/Recommendation

Consider in any order

4-6 weeks at treatment dose

**FURTHER LINE & CHRONIC DEPRESSION**

[**Combination**](#Combination) **of different antidepressants**

* [SSRI](#SSRIvenlafaxineDuloxetineMirtazapine" \o "SSRI or venlafaxine or duloxetine + mirtazapine) **[or](#SSRIvenlafaxineDuloxetineMirtazapine" \o "SSRI or venlafaxine or duloxetine + mirtazapine)** [SNRI + Mirtazapine](#SSRIvenlafaxineDuloxetineMirtazapine" \o "SSRI or venlafaxine or duloxetine + mirtazapine) **[(N)](#SSRIvenlafaxineDuloxetineMirtazapine" \o "SSRI or venlafaxine or duloxetine + mirtazapine)**
* [Mirtazapine **or** SSRI + Reboxetine](#MirtazapineorSSRIplusReboxetine) (2-8 mg daily)

**Mood Stabiliser** [**AUGMENTATION**](#Augmentation) **of partially effective antidepressants**

* [Lithium](#Lithium)\* **(N)** – aim for 0.4-0.8 mmol/L initially
* Lamotrigine (off-label) **(N)**

**Alternative MONOTHERAPIES**

* Moclobemide\* **(N)**
* Phenelzine\* **(N)**
* TriCyclic Antidepressant (TCA) **(N)**

**Antipsychotic AUGMENTATION of partially effective antidepressants**

* [Quetiapine immediate release](#Quetiapine) (150-300 mg/day) (off-label) **(N)** (1st line for psychotic depression)
* [Aripiprazole](#Aripiprazole) (2-20 mg/day) (off-label) **(N)**
* Olanzapine (5-15 mg/day) (off-label) **(N)** (1st line for psychotic depression)
* Risperidone (0.5-3 mg/day) (off-label) **(N)**
* [Amisulpride](#Amisulpride) (low dose: 50 mg/day) (off-label) **(N)**

**PSYCHOTIC DEPRESSION**

[**Agomelatine**](#Agomelatine)(if 3 previous failed or non-tolerated trials)

## Further Information About Treatment Options



## Consultation and Prescribing Advice General References

 

## Medication reviews

At each review, and at least annually, consider/assess:

* Therapeutic response to the medication including severity & frequency of depressive episodes
* Medication adherence
* Medication side effects (use a validated rating scale, e.g. PhQ9, BDI, HADS, HAM-D, QIDS-SR16, MADRS)
* Comorbid physical and psychiatric conditions
* Use of alcohol and other substances

### Useful links

**NICE Guidelines for Depression**

Depression in adults: recognition and management. 2022. (NICE guideline 222) [www.nice.org.uk/guidance/ng222](http://www.nice.org.uk/guidance/ng222)

Depression in adults with a chronic physical health problem: treatment and management. 2009. (Clinical guideline 91.) [www.nice.org.uk/guidance/cg91](http://www.nice.org.uk/guidance/cg91)

**The Maudsley Prescribing Guidelines**

Taylor, D., Barnes T.R.E. & Young A.H. (2021). Chapter 3 – Depression and anxiety. In The Maudsley Prescribing Guidelines, 14th Edition. London: John Wiley and Sons.

[lib.myilibrary.com/Open.aspx](http://lib.myilibrary.com/Open.aspx?id=786015&src=0) - *You will need an Athens account and login to access this link and can gain one through library services at the Trust if you do not already have one.*

Sections:

* *Antidepressants: relative adverse effects – a rough guide* – Table 3.26, p421-422
* *Antidepressant withdrawal symptoms* – p343-346
* *Serotonin syndrome symptoms* – p337
* *Antidepressants – swapping and stopping* – Table 3.7, p338-341

**Medication Information**

The Choice and Medication website has helpful information in agreeing choice of antidepressant with patients [www.choiceandmedication.org.uk/tees-esk-and-wear-valleys/](http://www.choiceandmedication.org.uk/tees-esk-and-wear-valleys/) and you can print out medication information sheets. It also has information on driving whilst taking medication.

**Switching between antidepressants**

In addition to the guidance embedded above, the NHS Specialist Pharmacy Service provides useful advice here: <https://www.sps.nhs.uk/category/specialty/mental-health-and-illness/>

Appendix: **Antidepressant De-prescribing Guidance**

Depression is a major public problem and medications are a common and effective treatment strategy. Continuing medication after the resolution of acute symptoms reduces the risk of relapse by around 50% however the optimum duration of treatment remains uncertain. Current guidelines recommend:

* Single episode Depression – Treat for 6-9 months
* Second episode – Treat for 1-3 years
* Third episode – Treat for at least 5 years
* Forth (and subsequent) episodes – Treat long-term (potentially life-long)

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.

Review

**STEP 1: SHOULD I DEPRESCRIBE? – Deprescribing triggers**

Inappropriate indication, no current indication, TCAs in older people, presence or risk of adverse events, drug interaction, drug-disease interaction, high drug burden index (DBI), poor adherence, or patient preference

**1a. Is there a documented indication or symptoms supporting continued use?**

**Inappropriate indication for continued use:**

No current depression >6 months

Consult/review with mental health specialist if applicable.

**Do not deprescribe if:**

* Recurrent or severe depression or other psychiatric condition such as 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?**

See Evidence-based advice in the appendix for additional information on risks of harm and benefits of continued use.

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, discussion and shared decision making, the patient or carer has communicated that they would like to proceed with or decline the deprescribing recommendation.

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 therapy. See Alternative management recommendations.
* Reduce dose slowly by 25-50% of the daily dose every 2-4 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 appendix 2)
* 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.

**3a) How to wean.**

**Initiation**

* Reduce dose slowly by 25-50% of the daily dose every 2-4 weeks.

**Adjust according to response.**

* If no discontinuation effects occur, continue to wean, and stop.
* Consider slower weaning (e.g. 12.5%) when reducing to the final lowest dose
* End treatment 2 weeks after administering the lowest dose.
* Consider alternate day dosing to 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

Monitor

**STEP 4: MONITORING**

* 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
* 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

**1-3 Days**

Discontinuation symptoms usually occur shortly after dose reductions

**>7 Days**

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

**NON-PHARMACOLOGICAL SUPPORT**

Medication is not first-line for many mental health conditions and there are multiple evidence-based non-pharmacological interventions available.

Consider:

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

Alternative Management

**Example De-prescribing Plan**

**Recommend non-pharmacological therapy to reduce reliance on antidepressants**

**Recommend gradually reducing to** **e.g. citalopram 15mg daily for e.g. 1 week and reassess,**

**then reduce to e.g. citalopram 10mg daily for e.g. 1 week and reassess,**

**then reduce e.g. citalopram 5mg daily for e.g. 1 week and reassess,**

**then reduce to e.g. citalopram 2.5mg daily for e.g. 1 week and stop.**

**Follow up with clinician e.g. fortnightly after discontinuation**

**Example Slower De-prescribing Plan**

**Recommend non-pharmacological therapy to reduce reliance on antidepressants**

**Recommend gradually reducing to e.g. Sertraline 150mg daily for e.g. 4 weeks and reassess,**

**then reduce to e.g** **Sertraline 100mg daily for e.g. 4 weeks and reassess,**

**then reduce e.g. Sertraline 50mg daily for e.g. 4 weeks and reassess,**

**then reduce to e.g. Sertraline 25mg daily for e.g. 4 weeks and stop.**

**Follow up with clinician e.g. fortnightly after discontinuation**

**Potential types of discontinuation effects**

|  |  |  |
| --- | --- | --- |
| **Physical symptoms**  | **Sleep symptoms**  | **Emotional symptoms**  |
| Nausea  | Insomnia  | Anxiety  |
| Headache  | Increased dreaming  | Depression  |
| Dizziness  | Vivid dreams  | Panic  |
| Abdominal cramps  | Nightmares  | Agitation  |
| Diarrhoea  |  | Irritability  |
| Fatigue  |  | Mood changes  |
| Flu-like symptoms  |  |  |
| Electric shock sensations (‘zaps’)  |  |  |
| Loss of appetite  |  |  |
| Visual disturbances (double vision; visual trailing)  |  |
| Palpitations  |  |  |
| Missed beats  |  |  |
| Sweating  |  |  |
| Flushing  |  |  |
| Tremor  |  |  |
| Tinnitus  |  |  |
| A feeling of inner restlessness and inability to stay still (akathisia)  |  |

**Risk of discontinuation effects with individual antidepressants**

|  |  |  |  |
| --- | --- | --- | --- |
| **Highest risk** | **Moderate risk** | **Low risk** | **Lowest risk** |
| Amitriptyline | Citalopram | Bupropion | Agomelatine |
| Clomipramine | Escitalopram | Fluoxetine |  |
| Paroxetine | Fluvoxamine |  |  |
| Venlafaxine | Imipramine |  |  |
| Duloxetine | Lofepramine |  |  |
|  | Nortriptyline |  |  |
|  | Mirtazapine |  |  |
|  | Reboxetine |  |  |
|  | Sertraline |  |  |
|  | Trazodone |  |  |
|  | Vortioxetine |  |  |

Above tables from: [Stopping antidepressants | Royal College of Psychiatrists (rcpsych.ac.uk)](https://www.rcpsych.ac.uk/mental-health/treatments-and-wellbeing/stopping-antidepressants)

**Patient Information Leaflets**

Royal College of Psychiatrists – [Stopping Antidepressants](https://www.rcpsych.ac.uk/docs/default-source/mental-health/treatments-and-wellbeing/print-outs/stopping-antidepressant-printable.pdf?sfvrsn=2c9a63e0_2)

Choice and Medication

Handy Fact Sheet: Coming off antidepressants

[1-Page Version](http://www.choiceandmedication.org/tees-esk-and-wear-valleys/generate/handyfactsheetstoppingantidepressantshighlightsuk.pdf) [2-Page Version](http://www.choiceandmedication.org/tees-esk-and-wear-valleys/generate/handyfactsheetstoppingantidepressantsuk.pdf)

Drug-specific fact sheets

[Citalopram](http://www.choiceandmedication.org/tees-esk-and-wear-valleys/generate/handyfactsheetcomingoffcitalopramuk.pdf) [Escitalopram](http://www.choiceandmedication.org/tees-esk-and-wear-valleys/generate/handyfactsheetcomingoffescitalopramuk.pdf) [Fluoxetine](http://www.choiceandmedication.org/tees-esk-and-wear-valleys/generate/handyfactsheetcomingofffluoxetineuk.pdf) [Paroxetine](http://www.choiceandmedication.org/tees-esk-and-wear-valleys/generate/handyfactsheetcomingoffparoxetineuk.pdf) [Sertraline](https://www.choiceandmedication.org/tees-esk-and-wear-valleys/generate/handyfactsheetcomingoffsertralineuk.pdf)

**Evidence Base**

A Cochrane meta-analysis of studies predominantly lasting 6-8 weeks, estimated that seven patients with depression needed to be treated with a SSRI in order to obtain a benefit in one (number needed to treat [NNT] = 7). Whereas, compared to placebo, 20-90 patients needed to be treated with a SSRI in order to suffer harm (withdrawal due to side effects) (number needed to harm [NNH] = 20-90)(Arroll, et al. 2009).

Continuing antidepressants after resolution of acute symptoms reduces the odds of depressive relapse by around two-thirds, which is approximately equivalent to a halving of the absolute risk (Geddes JR et al. 2003, Glue P et al. 2010). The risk of recurrence after the first episode of depression (after stopping 2 years of maintenance therapy) is approximately 60% over 2 years (AMH Aged Care Companion 2018).

Cognitive therapy has shown to be at least as effective in major depression as antidepressants, with sustained effects (DeRubis et al. 2005, Zhang et al. 2018). Low-certainty evidence suggests psychological support during while discontinuing antidepressants may be equivalent to continuing antidepressants on preventing depressive relapse (HR 0.89, 95% CI 0.66 to 1.19) and may result in successful discontinuation rates of 40% to 75% (Van Leeuwen et al. 2021).

It is uncertain whether continued or maintained pharmacotherapy (or both) with the reviewed antidepressant agents is a robust treatment for preventing relapse and recurrence in adults with persistent depressive disorder (Machmutow et al. 2019).

Overall, there is currently a lack of quality evidence generally exploring the relationship with respect to withdrawal, relapse, and adverse effects (Van Leeuwen et al. 2021).

**References**

This guidance is primarily adapted from guidance produced by New South Wales Therapeutic Advisory Group, which is available online at: <https://www.nswtag.org.au/deprescribing-tools/>

AMH Aged Care Companion: Major depressive disorder. 2018.

Arroll B, Elley CR, Fishman T, et al. Antidepressants versus placebo for depression in primary care. Cochrane Database of Sys Rev. 2009; 3: CD007954

Bazire S. Psychotropic Drug Directory 2020/21

DeRubis RJ, Hollon SD, Amsterdam JD, et al. Cognitive therapy vs medication in the treatment of moderate to severe depression. Arch Gen Psychiatry. 2005; 62(4): 409-416.

Hilmer SN, Mager DE, Simonsick EM, et al. A drug burden index to define the functional burden of medications in older people. Arch Intern Med. 2007; 167(8):781-787. Available at <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/412262>.

Frank et al. Three-year outcomes for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1990; 47: 1093-9

Geddes JR et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet 2003; 361:653–661.

Glue P et al. Meta‐analysis of relapse prevention antidepressant trials in depressive disorders. Aust N Z J Psychiatry 2010; 44:697–705

Kupfer et al. Five-year outcome for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1992; 49: 769-73

Machmutow K, Meister R, Jansen A, Kriston L, Watzke B, Härter MC, Liebherz S. Comparative effectiveness of continuation and maintenance treatments for persistent depressive disorder in adults. Cochrane Database of Systematic Reviews 2019, Issue 5.

NICE (2022) Depression in adults: recognition and management. Available online at [www.nice.org.uk/guidance/ng222](http://www.nice.org.uk/guidance/ng222)

Taylor D et al. Prescribing Guidelines in Psychiatry 14th Edition

Reeve E, Wiese MD, Hendrix I, et al. People’s attitudes, beliefs, and experiences regarding polypharmacy and willingness to deprescribe. J Am Geriatr Soc. 2013; 61(9):1508-1514.

Van Leeuwen E, Driel ML, Horowitz MA, Kendrick T, Donald M, De Sutter AIM, Robertson L, Christiaens T. Approaches for discontinuation versus continuation of long‐term antidepressant use for depressive and anxiety disorders in adults. Cochrane Database of Systematic Reviews 2021, Issue 4.

Zhang Z, Zhang L, Zhang G, et al. The effect of CBT and its modifications for relapse prevention in major depressive disorder: a systematic review and meta-analysis. *BMC Psychiatry*. 2018; 18(1):50.