Antidepressants:
Quality prescribing advice for adults

Foreword

Antidepressant prescribing continues to increase. In part, this is due to a range of antidepressants being available and used to treat various conditions: depression, neuropathic pain, anxiety disorders and other conditions. As well as positive changes in the public's attitudes towards mental health conditions. More recently the number of people receiving long-term antidepressant treatment has increased, some of which will be appropriately providing people with better courses of treatment and enabling better outcomes. However, some of the increased long-term use may be inappropriate as it is known that the frequency of proactive review of these medicines, when people are not experiencing crises, reduces with time.

This antidepressant prescribing advice is primarily intended to support healthcare professionals and others to encourage the appropriate use of antidepressants. Secondly, it is intended to support and enable the appropriate reduction of ineffective medicines, or where people have completed a course of treatment, by supporting and enabling proactive patient-centred reviews and appropriate continuation, reduction and discontinuation of antidepressants to minimise avoidable drug-related harms.

This advice is not intended to override other non-pharmacological and/or pharmacological prescribing treatment advice such as NICE, British Association for Psychopharmacology (BAP), Polypharmacy: Realistic Prescribing Guidance [link] or the principles outline in the Realising Realistic Medicines report, but to complement and add practical advice and options, for tailoring care to the needs and preferences of the individual.

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Key contributions.
The lead author was Chris F Johnson

Short-Life Working Group

Ailsa Stein
Alastair Cook
Alpana Mair
Amy Comrie
Andrew Walker
Ann Wales
Amy Comrie
Beth Crozier
Blair Smith
Chris F Johnson
Claire Campbell
David Revie
Denise McFarlane
Donald Macintyre
Duncan Hill
Kieran Dinwoodie
Iain Wilson
Irene Oldfather
Jackie Wiggins
Laura Wilson
Lesley Colvin
Lise Hertel
Margaret Umeed
Paul Paxton
Stephanie Cymber
Stuart Law
Stuart McTaggart

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[Add as appropriate]

Abbreviations

A&A	Ayrshire and Arran Health Board
BAP	British Association for Psychopharmacology
B-Z	Benzodiazepines and/or z-hypnotics
CBT	Cognitive Behavioural Therapy
cCBT	computerised Cognitive Behavioural Therapy
D&G	Dumfries and Galloway Health Board
DOAC	Direct oral anticoagulant
FV	Forth Valley Health Board
GGC	Greater Glasgow and Clyde Health Board
HSCP	Health and Social Care Partnership
ISD	Information Service Division
MR	Modified Release
MAOI	Monoamine oxidase inhibitor
NICE	National Institute for Clinical Excellence
NSAID	Non-steroidal anti-inflammatory drug
PHQ-9	Patient Health Questionnaire
SNRI	Serotonin and noradrenaline re-uptake inhibitor
SSRI	Selective serotonin re-uptake inhibitor
TCA	Tricyclic antidepressant
WI	Western Isles Health Board

Contents

1. Executive summary - main points

This prescribing advice:

- Does not override existing local and national guidelines for the treatment and management of pain or common mental health disorders [see Background].

- Recommends that non-medicalised and evidence based psychological interventions should be considered where appropriate and in line with current clinical guidelines [see Recommendations].

- Recommends supportive and collaborative discussions between individual's and prescribers when reviewing antidepressants and considering ongoing needs. That individual's concerns and preferences regarding the reduction and/or cessation of antidepressants are considered in order to tailor individualised treatment plans.

And that:

- The clinical records for people receiving antidepressant prescriptions should be appropriately Read coded, with the indication for the antidepressant [see Recommendations].

- Electronic clinical systems to be used as part of routine practice to enable easy identification of people for proactive medication reviews with a pre-planned review date [see Recommendations].

- People prescribed antidepressants, or any other medicine, are encouraged to initiate discussions regarding the appropriate continuation, reduction and discontinuation of pharmacological treatment [see Recommendations].

- Practitioners should proactively review antidepressant use and need when individuals are stable and well, and that the following groups of people may be appropriate for proactive reviews, Table 1 [see Targeting reviews].

- The 7-steps medication review process may support clinicians with a proactive person-centred medication review [see 7-steps].

- Different strategies for reducing and stopping antidepressants should be considered and applied depending on an individual's preferences and needs [see Reducing and stopping].

Table 1, Potential groups of people that receive antidepressants and may benefit being prioritised for regular proactive medicines review

- People receiving the same antidepressant continuously, long-term (≥2 years)

- Older adults (≥65 years) and/or frail adults
  - Receiving a SSRI plus antiplatelet/NSAIDs/DOAC/warfarin without gastro-protection, due to the increased risk of gastric bleed with this combination.
  - Receiving >1 defined daily dose per day of citalopram (>20mg per day) or escitalopram (>10mg per day) due to QTc prolongation.
  - Diagnosed with dementia, as antidepressants may provide limited antidepressant effects.
  - Receiving TCAs and other anticholinergics – reduce the anticholinergic drug burden, to reduce the risk of falls and confusion.

- People receiving combinations:
  - Antidepressant plus long-term (≥8 weeks) benzodiazepines and/or z-hypnotics (B-Zs)
    - B-Zs are associated with an increased risk of depressive symptoms, paradoxically worsen anxiety, and reducing the effectiveness of psychological treatments. Reviewing reducing B-Z use prior to assessing antidepressant need may be appropriate.
    - B-Zs prescribing and use is associated with the use of higher doses of SSRIs
  - Combination antidepressant treatment e.g. mirtazapine with SSRI/SNRI. There is a lack of evidence demonstrating the efficacy of this combination to treat depression. People initiated on combinations by psychiatry should be reviewed by specialist services.
  - Higher risk of QTc prolongation combinations:
    - Citalopram or escitalopram or TCAs plus: methadone, antipsychotics, antinausea, quinine, etc

- People receiving high dose SSRIs for the treatment of depression.

- People receiving low dose mirtazapine or trazodone: for insomnia or subtherapeutic doses of mirtazapine (<30mg per day) for the treatment of depression.

DOAC: direct oral anticoagulant. NSAID: non-steroidal anti-inflammatory drug. SSRI: selective serotonin re-uptake inhibitor. TCA: Tricyclic antidepressant
QTc prolongation see end of Section 2.5 for more information [link]

2. Background

[Return to Main points]

2.1. What is the purpose of this advice?

This advice is intended to support healthcare professionals and others to facilitate the appropriate use of antidepressants. It is not intended to override other prescribing and treatment advice such as NICE, British Association for Psychopharmacology (BAP), Polypharmacy: Realistic Prescribing Guidance [link] or the principles outline in the Realising Realistic Medicines report, but to complement and add practical advice and options for tailoring care to the needs and preferences of individual's.

As antidepressants are used for a variety of conditions and are commonly prescribed for people experiencing a range of co-morbidities and diseases. This prescribing advice differs from previous guidance, as it provides a range of options for individual's and clinicians to support proactive patient-centred antidepressant reviews; from antidepressant initiation to cessation and post-treatment follow up period, and includes advice for treatment plans, managed reductions, and discontinuation as appropriate for adults.

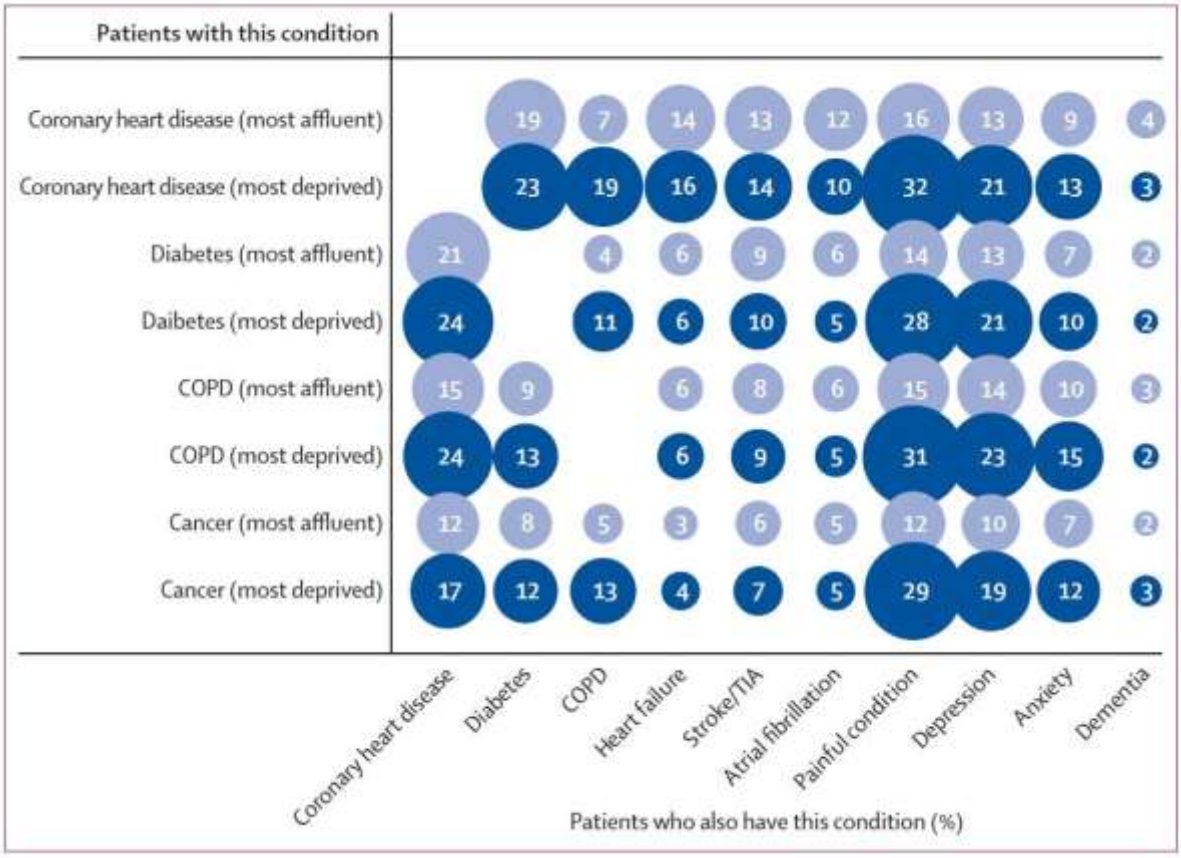
2.2. What is the benefit of this prescribing advice to the person receiving an antidepressant?

This quality prescribing advice is intended to encourage supportive and constructive discussions between individual's and prescribers when reviewing antidepressants and ongoing need, and where appropriate, consider the fears and apprehensions associated with reducing/stopping antidepressants whilst tailoring treatment to the individual's needs.

As with all medicines – not just antidepressants – it is important to routinely and proactively monitor and review the ongoing needs and rationale for continued use. However, we know that long-term antidepressant use is increasing,[1,2] and that the longer someone receives an antidepressant the less frequently it or the condition it is treating is reviewed.[3,4] This may and can lead to inappropriate long-term prescribing for some individuals.

Other potential benefits of proactive reviews are that as a large proportion of people with depression (receiving an antidepressant) have co-morbidities such as diabetes, cardiovascular disease, respiratory disease (Figure 1), and may also receive multiple prescribed medicines (known as polypharmacy).[5,6] They may also be frail and more likely to experience adverse drug effects and avoidable harms (see Section 2.5 and Figure 5). Therefore, proactively reviewing antidepressants creates an opportunity for a planned holistic patient-centred assessment and review of conditions and medicine needs that may help to reduce avoidable drug-related harms.

Figure 1. Comorbidities comparison between most affluent and most deprived deciles.[5]



It is also known that some prescribers may be less comfortable reviewing psychotropic medicines such as antidepressants and that individuals may be fearful of reducing and stopping antidepressants. This may be due to concerns about relapsing or recurrence of their illness, and/or experiencing antidepressant discontinuation/withdrawal symptoms, all of which may result in inappropriate long-term antidepressant treatment.[4,7-12]

Overall, proactive medicines reviews will help to:

- Reduce inappropriate medicines use;
- Reduce avoidable adverse drug effects and harms (see Section 2.5 and Figure 5)
- Optimise care and outcomes; and
- Enable people to take the medicines they need.

Proactive medicines reviews will also create an opportunity for people to access and be directed to other non-pharmacological including psychological interventions which may be appropriate and/or needed to achieve better longer-term outcomes.[13,14] Where appropriate, and when applied to practice, the prescribing advice may help to provide structure to support people who are anxious about reducing and/or stopping their antidepressant therapy.

Discontinuation symptoms or 'withdrawal effects'?

The term 'discontinuation symptoms' is used to describe symptoms experienced on stopping medicines that are not drugs of dependence, although there are important semantic differences in the terms 'discontinuation' and 'withdrawal' symptoms – the latter implying addiction, the former does not.[15] While the distinction is important for precise medical terminology, it is irrelevant when it comes to personal experiences and how an individual may describe their signs and symptoms. Regardless of the semantics, proactive medicines reviews create an opportunity for individuals and prescribers to discuss and address potential fears and worries, alongside developing appropriate management plans for the use of antidepressants and other medicines as part of a realistic prescribing plan.

2.3. What are the benefits of this prescribing advice to healthcare professionals?

Prescribers have identified and reported that it can be,

'...easier to start [psychotropic medicines] than to stop [them],'[7]

and that

'… we're [prescribers] probably not good enough, at the moment, is sort of the long-term managing and the coming-off part.'[11]

In part, this may be due to a range of perceived and actual barriers, such as some healthcare professionals lacking confidence, knowledge and skills to support and enable proactive antidepressant review and discontinuation, as well as individuals getting lost in 'the system'.[7,11,16] First, some electronic clinical systems routinely used in clinical practice may be limited in enabling prescribers to proactively identify people for review. However, the Scottish Therapeutics Utility (STU) has been developed for use in general practice, in Scotland, to help identify people who may benefit from a proactive medication review. General practice staff can routinely use STU to identify and plan antidepressant review work. Secondly, while there is no consensus on the optimal method for antidepressant withdrawal,[17,18] this guidance provides a range of options for reducing and withdrawing antidepressants [Section 6].

For the treatment of depression some prescribers wait 8 weeks or more before optimising doses or switching antidepressant treatments in poor or non-responders.[4,19] Antidepressants demonstrate their effects within 1-2 weeks of use.[15,20]

This prescribing advice therefore, provides practical structured advice and examples of good practice approaches for identifying individuals, reviewing antidepressant therapy and routinely supporting people in our care.

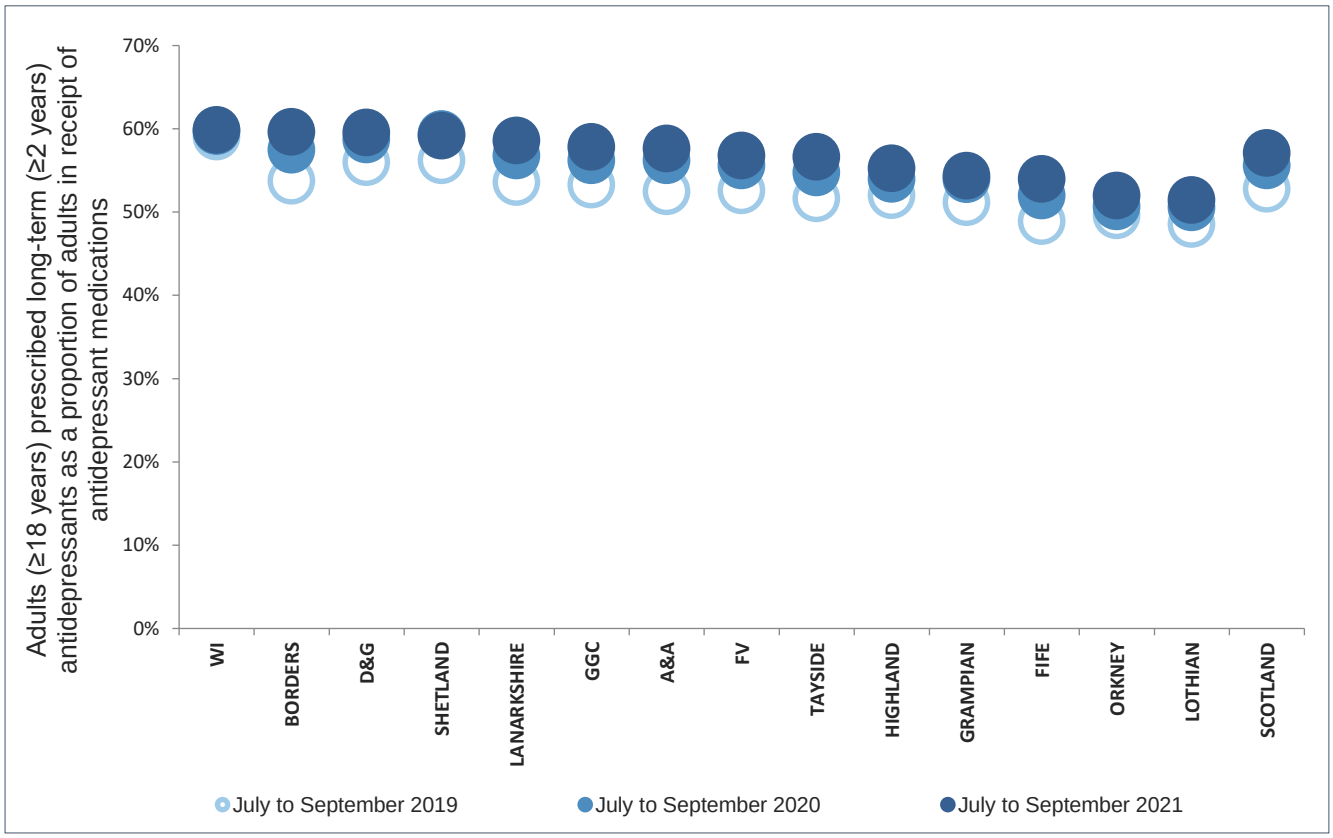
2.4. What are the benefits of this prescribing advice to organisations?

Implementation and use of this advice will help improve patient care and outcomes. Included within this document is a range of prescribing indicators and measures which can help focus attention and resources on areas that would benefit from proactive action. These measures will be of use to Health Boards, Health and Social Care Partnerships (HSCPs), General Practice Clusters and individual general practices. The resources are available within this document, as well as case studies and examples of what has already been trialled.

2.5. Why is proactively reviewing antidepressants use important?

In Scotland, as with other Westernised societies, antidepressant prescribing has increased substantially over the last 50 years and continues to increase. In part, this has been due to the availability of different antidepressants,[21,22] some of which are better tolerated and safer than others;[23,24] people's expectations[25,26] and changes in the society's attitudes towards mental health conditions;[27] greater willingness to prescribe for a variety of mental health and non-mental health conditions;[28-30] increased long-term use;[1]and use of higher doses;[13,31] lack of regular medicine reviews;[4,32] and more people receiving antidepressant therapy, with 1 in 5 adults receive one or more antidepressant prescriptions in a year, and more than half of those (6 in 10 adults) receiving long-term (≥2 years) treatment (Figure 2).[33]

Figure 2, Adults (≥18 years old) prescribed long-term (≥2 years) antidepressants as a proportion of adults in receipt of antidepressant medications, by health board



NHS Board	July to Sept 2019	July to Sept 2020	July to Sept 2021
Western Isles	59.0%	59.7%	59.8%
Borders	53.7%	57.4%	59.6%
Dumfries & Galloway (D&G)	56.0%	58.7%	59.5%
Shetland	56.2%	59.3%	59.1%
Lanarkshire	53.6%	56.8%	58.6%
Greater Glasgow & Clyde (GGC)	53.3%	56.2%	57.8%
Ayrshire & Arran (A&A)	52.4%	56.2%	57.6%
Fourth Valley (FV)	52.6%	55.6%	56.7%
Tayside	51.6%	54.7%	56.6%
Highland	52.0%	53.9%	55.2%
Grampian	51.1%	53.9%	54.4%
Fife	48.9%	52.0%	53.9%
Orkney	49.6%	50.7%	52.0%
Lothian	48.5%	50.5%	51.4%
Scotland	**52.8%**	**55.6%**	**57.1%**

While the majority of antidepressants are prescribed for the treatment of 'common mental health conditions' such as depression and anxiety disorders, they are usually only one aspect of a complex multidimensional treatment plan to care for and support people to achieve recovery.[20,34] The lack of regular review reduces the opportunity to advise the use of non-pharmacological approaches that may aid in recovery and can lead to inappropriate long-term antidepressant use.[4,16,32]

Long-term antidepressant use is associated with the use of higher antidepressant doses (Figure 3), and whil this may be appropriate for some antidepressants, it can be inappropriate for others. For example:

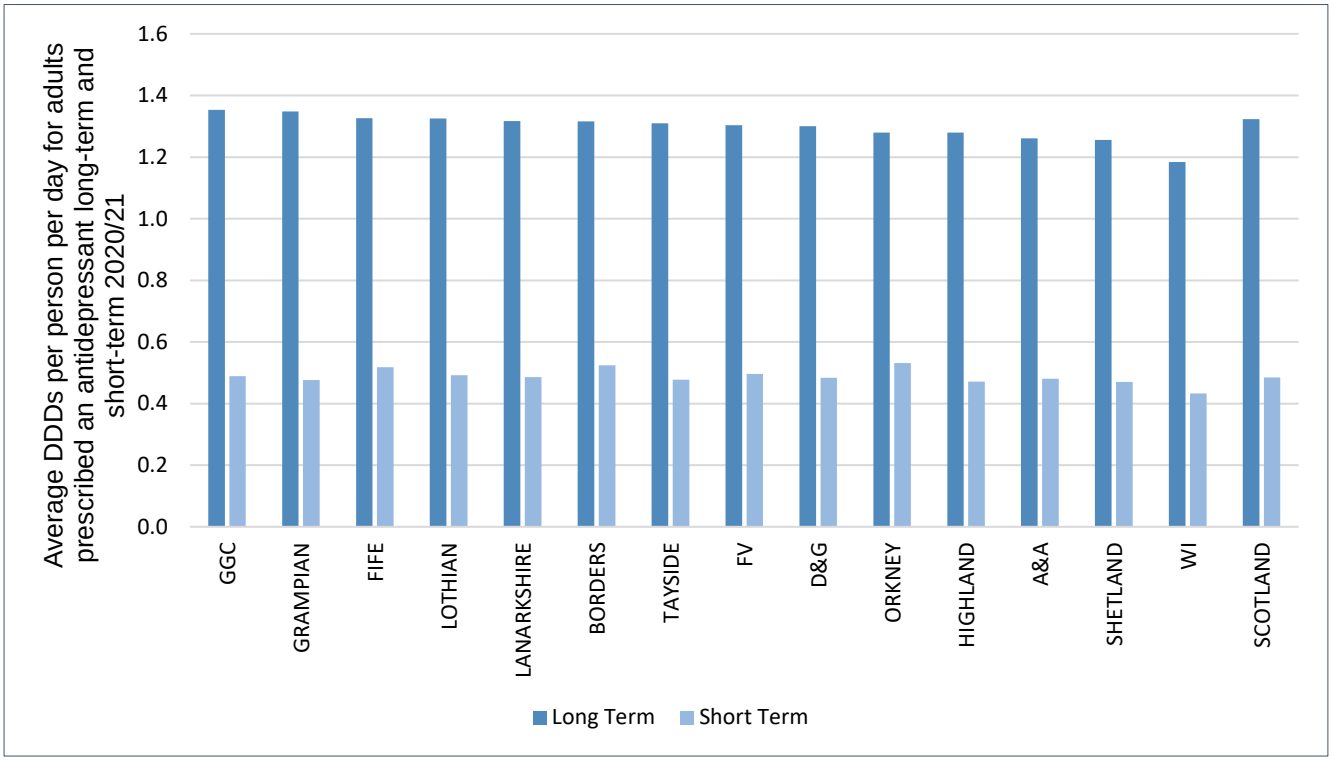
- Selective serotonin re-uptake inhibitors (SSRIs) demonstrate a flat dose-response curve for the treatment of depression. Standard daily doses: 20mg citalopram/fluoxetine/paroxetine, 50mg daily of sertraline or 10mg escitalopram – provide optimal antidepressant effectiveness – *'20's plenty and 50's enough'*.[20,35-37] As individuals may not be proactively reviewed when stable and well, presenting only at times of crisis, this may lead to doses being inappropriately increased in response to the crisis.[4] For SSRIs, higher than standard doses are known to cause more adverse effects and avoidable harms (i.e. anxiety, insomnia, falls, etc) and are possibly associated with more withdrawal effects.[20,35-38] In addition higher than standard doses are not more effective at reducing depressive symptoms in poor and/or non-responders.[37,39-41]
- Mirtazapine also demonstrates optimal effects for the treatment of depression at 30mg daily,[36] however its use is associated with 5-7 kg weight gain.[42,43] Lower doses (15mg daily) are more sedating.[44]
- Tricyclics antidepressants (TCAs) demonstrate a dose-response for the treatment of depression where higher doses can be more effective e.g. increasing to 100mg to 125mg per day.[15,20,35] However, doses as low as 10mg daily can be effective for the treatment of neuropathic pain while 50mg to 75mg daily provide optimal effects for the majority of people.[30,45] Again, higher doses are known to cause more adverse drug effects and avoidable harms such as sedation, confusion and QTc prolongation[a], amongst others.
- Serotonin and noradrenaline re-uptake inhibitors (SNRIs) demonstrate a dose-response effect for the treatment of depression where higher doses can be more effective.[35,36,44,47-49] For example, venlafaxine exhibits predominantly serotonin ceiling effects at doses <150mg daily, with noradrenaline (>150mg daily), and dopamine (>225mg daily) effects becoming more significant as doses are increased.[44,47] The SNRI Duloxetine demonstrates similar effects.[48,49] Once

[a] QTc prolongation: QTc prolongation is of concern as it is associated with ventricular tachycardia and sudden cardiac death. The QT interval on an electrocardiogram describes the manifestation of ventricular depolarization and repolarization. The QT interval is influenced by heart rate therefore the QT interval should be measured for rate correction, allowing the calculation of the corrected QT interval (QTc). Intervals of 440 to 460 milliseconds in men and 440 to 470 milliseconds in women are considered to be at the top limit of normal range. Bazett's formula is considered the gold standard for QTc calculation. QTc prolongation is associated with ventricular tachycardia and sudden cardiac death.46

again higher doses are known to cause more adverse drug effects and avoidable harms including insomnia, weight loss and sexual dysfunction.[36,50,51]

While in certain conditions it may be appropriate to increase the antidepressant dose, prescribers should always consider drug limitations and the risks associated with the use of higher doses of medicines. Proactive review of individuals when their condition is stable creates an opportunity to review the need for continued antidepressant treatment regardless of the indication for use to reduce inappropriate or ineffective antidepressant use.

Figure 3, Average defined daily doses (DDDs) per person per day for adults (≥18 years old) prescribed an antidepressant long-term (≥2 years) or short-term (<2 years), by health board for 2020/21



All antidepressant classes are included. Note TCAs are more commonly prescribed for the treatment of neuropathic pain (e.g. amitriptyline 10-50mg daily – 0.1 to 0.7 DDD) rather than depression (100-150mg daily – 1.3 to 2 DDD). The majority of SSRIs however, are prescribed for the treatment of depression (e.g. citalopram 20mg to 40mg daily – 1 to 2 DDD).

NHS Board	Long-term (≥2 years)	Short Term (<2 years)
Greater Glasgow & Clyde (GGC)	1.35	0.48
Grampian	1.35	0.49
Fife	1.33	0.52
Lothian	1.33	0.49
Lanarkshire	1.32	0.49
Borders	1.32	0.52
Tayside	1.31	0.48
Fourth Valley (FV)	1.30	0.50
Dumfries & Galloway (D&G)	1.30	0.48
Orkney	1.28	0.53
Highland	1.28	0.47
Ayrshire & Arran (A&A)	1.26	0.48
Shetland	1.26	0.47
Western Isles	1.18	0.43
Scotland	**1.32**	**0.48**

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3. Recommendations and guidance for healthcare professionals

3.1. Healthcare professionals should...

Ensure individuals are assessed and Read Coded for the condition being treated.

Only a minority of individuals have a clear electronically recorded (Read Code indication) for receiving an antidepressant.[52] Although the indication for antidepressant use can be identified from free-text entries in electronic and paper clinical notes, these are not easily identified, unless an individual's clinical record is accessed and specifically searched for.[6] Therefore, appropriately coding individuals' records would support easier identification of these individuals for proactive medication reviews in general practice and specialist services, as prescribers have indicated that:

'...patients can get lost in the system, and that systems which adequately prompt medication reviews would be useful in broaching discontinuation with patients.' [11]

Healthcare practitioners and clinical teams should ensure individuals are appropriately coded in their electronic clinical systems:

- Depression (code E2B), anxiety with depression (E2003), bipolar affective disorder (Eu32), etc.
- Chronic pain 1M52, neuropathic pain (N2423), diabetic neuropathic pain (1M8) and chronic pain review recorded as 66n when a review is undertaken
- Anxiety disorder such as generalised anxiety disorder (GAD, E2002), post-traumatic stress disorder (PTSD, Eu431), etc.
- Where the condition has resolved and the antidepressant has been stopped please use the appropriate Read Code e.g. Depression resolved (212S), anxiety resolved (2126J).[b]

As antidepressants are commonly used to treat neuropathic pain please also consider the principles outlined in the Chronic Pain guidance [link]

In relation to mental health and emotional distress, where appropriate complete and record a bio-psycho-social assessment including assessment of the risk of self-harm and/or suicide, and record the severity, as outlined in appropriate guidelines.[53,54] Consider and exclude physical causes of signs and symptoms. Consider: alcohol (FAST tool), substance misuse, bereavement, and exclude organic disease as a cause for symptoms. Continue to use and record the results of valid assessment tools such as PHQ-9, CORE 10 or other suitable rating scales to support continuity of care. As depression and other mental health conditions are associated with an increased risk of deliberate self-harm and suicide, ask individual's directly about

[b] Other Read Codes for resolution of symptoms are not currently available on general practice systems

thoughts/plans of self-harm and/or. Especially as it is known that, although some individuals may have suicidal thoughts when visiting their doctor they may withhold and not share their thoughts.[8,55] Where healthcare professionals are uncomfortable asking directly about self-harm and/or suicide, the PHQ-9 assessment tool includes a self-harm question that may help facilitate and enable discussion around self-harm and suicide. As outlined in guidelines, such as the NICE depression guidelines, antidepressant may be appropriate in treating depression as part of the Stepped-Care model for the treatment of moderate to severe depression [link].[56]

Develop a clear management plan collaboratively with the individual, and/or carer(s) if appropriate.

Aim to develop mutually supportive and constructive discussions between individual's and prescribers when reviewing antidepressants and ongoing treatment needs, and where appropriate consider the fears and apprehensions associated with reducing/stopping antidepressant therapy and tailor treatment to the individual's needs.

The Stepped-Care approach should be used to tailor the most appropriate intervention to the individual's needs. This can be done according to the severity of the condition being treated such as self-help, non-pharmacological or with or without antidepressants.[56-58]

Include realistic expectations and review dates; that can be Read Coded for recall and pre-planned follow up.

Non-medicalised and non-pharmacological options, including psychosocial and/or psychological interventions, should be encouraged and pursued where appropriate.

Non-medicalised and psychosocial[59-61]
While a range of activities may help with common mental health problems and pain management, these will vary with individual's preferences, capabilities, and locality. However, some of the following may be appropriate and should be considered and discussed before initiating an antidepressant, as well as when continuing an antidepressant for more severe illness. Where appropriate and available, Link workers may be able to support and enable individuals to access some of the below options

- Exercise and regular physical activity e.g. 30 minute walks.
- Debt advice and/or money management e.g. seeking advice from appropriate agencies such as Citizens Advice.
- Hobbies and interests e.g. gardening, crafts, etc.
- Work-life balance.
- Lunch clubs and other activities which may help to reduce social isolation.
- Discussing problems, where appropriate, with a close friend or confidante that is willing and able to listen.

Psychosocial and psychological Interventions
The Psychological Therapies Matrix (2015) [link] outlines a matched care approach to support the safe and effective delivery of evidence based psychological interventions. Both the Matrix and clinical guidelines advocate decisions regarding psychological interventions based on a comprehensive assessment of need and suitability, individual preferences, availability of trained practitioners and be culturally appropriate.[56-58] This matched care model considers 'high volume', low intensity interventions for mild to moderate symptoms, in addition to high intensity and highly specialist interventions delivered by practitioners with additional competences with access to appropriate supervision for those presenting with more complex presentations. The Matrix acknowledges those in general practice and primary care regularly identify and support those presenting with psychological issues and mental health disorders and are therefore in a position to provide support for low intensity interventions and referral to specialist mental health services where indicated.

Low Intensity Interventions
Low intensity interventions for mild to moderate symptoms of insomnia and anxiety include guided self-help and computerised Cognitive Behavioural Therapy (cCBT). Psychoeducation regarding the specific condition (anxiety, insomnia) can support self-management. A range of evidence based cCBT programmes and telephone supports are available to support general mental wellbeing, sleep problems (including insomnia) and mild to moderate symptoms of anxiety. Links to these programmes can be accessed via NHS Inform (Mental Health). Please refer to Appendix 1 and 2 for a detailed description and links to these resources.

High Intensity and Highly Specialist interventions
For those individuals who present with moderate to severe symptoms of anxiety and more complex presentations, including those set within the context of co-occurring substance use, a referral for High Intensity and/or Highly Specialist Interventions (including Cognitive Behaviour Therapy (CBT)) are indicated. These interventions are usually delivered within NHS or non-NHS[c] and/or specialist services.

Follow a clinically appropriate approach to initiating antidepressants:

A holistic, bio-psycho-social assessment that includes an assessment of the risks, benefits and limitations of prescribing, should inform decisions to initiate antidepressants, no matter what condition is being treated, whilst giving a consideration to the psychological components of care.

- Consider comorbidities as part of the bio-psycho-social assessment and the potential for interactions with other medicines and diseases e.g. QTc prolongation, etc. prior to initiating an antidepressant.
- Depression:

[c] Non-NHS services: Ensure Non-NHS practitioners providing psychological therapies are registered with appropriate professional bodies e.g. Health and Care Professions Council, British Association of Behavioural and Cognitive Psychotherapy, British Association of Counselling and Psychotherapy.

    - The Stepped-Care approach should be used to help choose the most appropriate intervention; self-help, non-pharmacological, with or without antidepressant therapy.[56]
    - Consider that 50% of individuals' depressive symptoms can spontaneously remit within 12 weeks of diagnosis.[62]
    - Mild depression (i.e. PHQ-9 score ≤14) responds better to non-pharmacological approaches; antidepressants are not effective for the treatment of mild depression.[20,56]
    - Moderate to severe depression. An appropriate antidepressant can be effective for reducing symptoms of depression and/or helping people achieve remission, especially when used as part of the Stepped-Care in combination with non-pharmacological treatment and/or self-help, see Figure 4.[20,56]
- Neuropathic pain:
    - Tricyclic antidepressants (TCAs) and duloxetine demonstrate modest effects for the treatment of neuropathic pain.[30]
- Anxiety disorders:
    - The Stepped-Care approach should be used to help choose the most appropriate intervention; self-help, non-pharmacological with or without antidepressants,[57,58] in supporting individual's to achieve a reduction in anxiety symptoms and/or achieve remission, see Figure 4.
    - Different antidepressants demonstrate variable efficacy depending on which anxiety disorder is being treated – generalized anxiety disorder (GAD), panic disorder, obsessive compulsive disorder (OCD), etc.[53,63]

Discuss: Individual's and prescriber expectations; Stepped-Care and Watchful-waiting for common mental health conditions; effective non-pharmacological interventions (e.g. exercise, physical activity, self-help, etc.); drug effects and limitations (e.g. dose-response) and dose ranges for treatment of different conditions (e.g. SSRI flat dose-response effects for depression: meaning that '20's plenty and 50's enough' – standard doses of 20mg daily of citalopram/fluoxetine/paroxetine or 50mg daily of sertraline – to provide the full antidepressant effect,[36,37,39] or neuropathic pain response to TCAs at doses ≤75mg per day);[30] and the potential short and long-term adverse drug effects (e.g. nausea, agitation, sedation, sexual dysfunction, etc.) Figure 5. It is also important to discuss and consider when and how the antidepressant will be reduced and stopped in the future to minimise potential drug-related harms.

Provide appropriate information about the condition (NHS Inform), antidepressant treatment and stopping. The Choice and Medications website contains a variety of information and leaflets which might be helpful.

Plan and agree follow up in relation to the condition being treated. In relation to depression, it is a widely held belief that antidepressants do not exert their effects for 4 to 6 weeks; however, all antidepressants show a pattern of response and rate of improvement which is greater in the first 1-2 weeks.[15,20,64] Therefore for those with no response at 3-4 weeks review: diagnosis; concordance with treatment; and where appropriate consider switching to an alternative antidepressant. Studies demonstrate that prescribers may change the antidepressant or optimise the dose at

8 weeks, which creates a lag in treatment and may slow recovery.[4,19] Where appropriate communicate changes in prescribing to the individual's specialist in secondary.

Agree, plan and record the criteria for reducing and stopping the antidepressant in the future, or if adverse drug effects become intolerable e.g. severe restlessness, and/or they experience more frequent thoughts of suicide or deliberate self-harm to them and others. Although younger people aged ≤25 years old are considered to be at greatest risk of antidepressant associated self-harm, there are multiple age, gender and regional effects that are associated with self-harm and suicide,[65,66] therefore this should be discussed.

Encourage people that are prescribed antidepressants, or any other medicine, to initiate open discussions regarding the appropriate continuation, reduction and discontinuation of pharmacological treatment.

Review effectiveness, tolerability and concordance on an ongoing basis, and where appropriate reduce the number and doses of medicines to minimise avoidable adverse effects and avoidable harms, and optimise concordance. Consider inviting individuals for proactive medication reviews. See Appendix 3 example review invite letter.

Figure 4, Interventions to aid reduction of symptoms and recovery

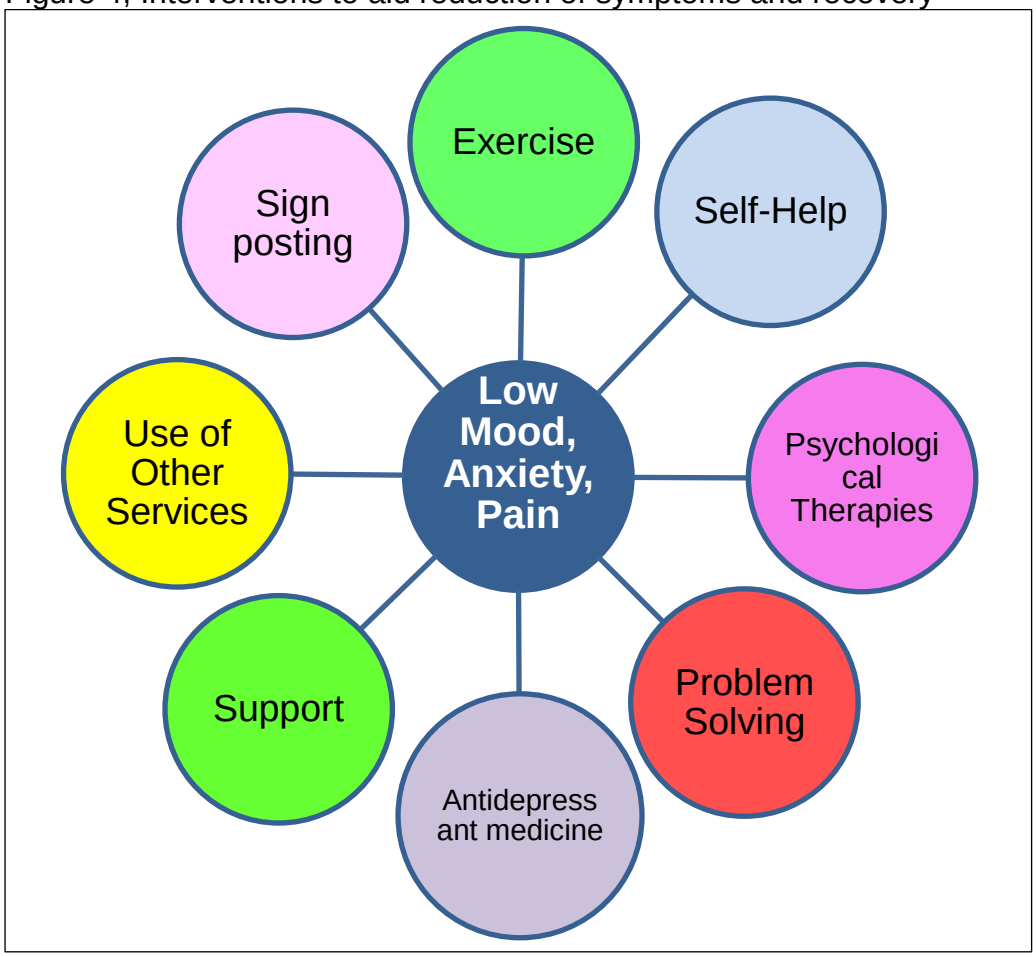
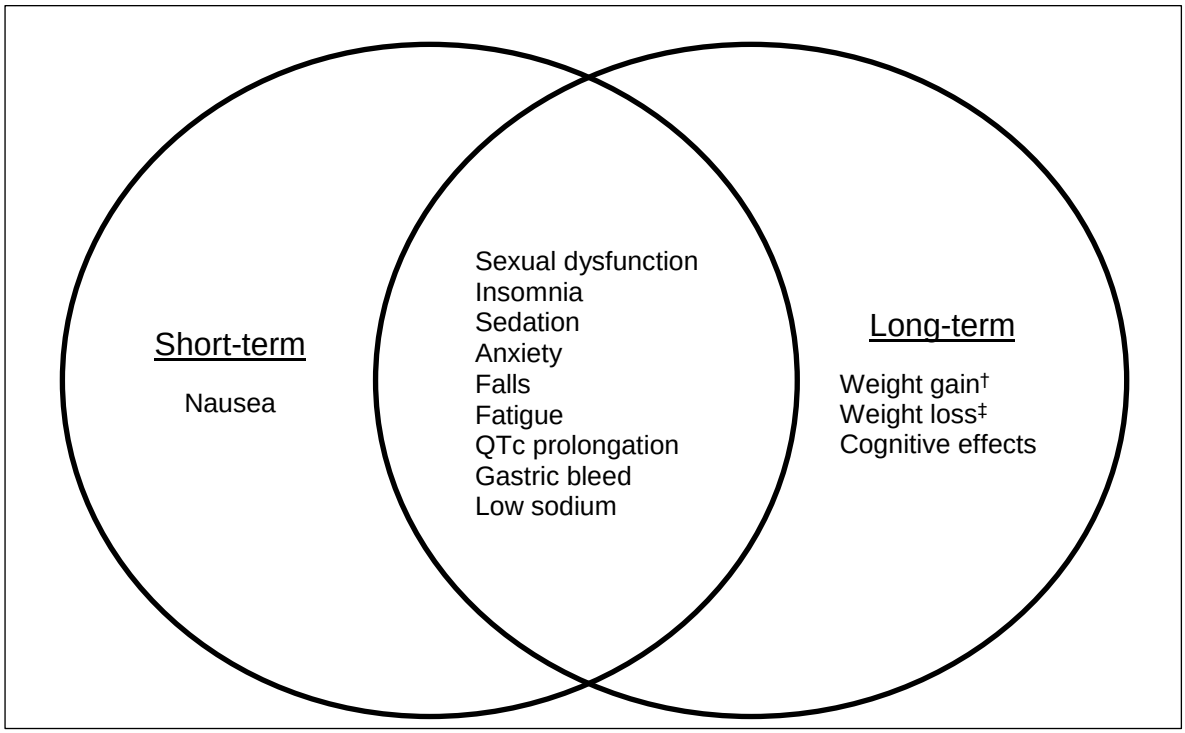


Figure 5, Common short-term and long-term adverse drug effects/harms



Note: Adapted from Papakostas 2007.[67] People may experience weight changes during antidepressant treatment. Weight gain may be associated with depression recovery and improved appetite on one hand and undesirable antidepressant effects on the other;[68] however, many placebo controlled studies report no weight data making it difficult to accurately estimate weight changes.[67] SSRIs have been seen as weight neutral, or in some cases associated with weight loss in the short-term (≤8wk studies) and weight gain in the long-term.[68]

† SSRIs, mirtazapine and antidepressant doses of TCAs.[RW.ERROR - Unable to find reference:21772]

‡ Venlafaxine.[RW.ERROR - Unable to find reference:21772]

3.2. Boards and HSCPs should...

Consider the prescribing advice within this document alongside local prescribing and clinical data; positions and trends, to plan, resource and drive quality improvement and prescribing initiatives.

Nominate local leads/champions – one medical and one within or with strong links to medicines management teams or equivalent – to drive delivery and recommendations within this document.

Consider and engage a whole system approach to delivering quality improvements in prescribing

- **Ensure primary and secondary care are informed**, to support continuity care and overall goals of reviewing and minimising inappropriate prescribing. Especially given the significant influence of secondary care.
- **Work with third sector (non-medicalised) organisations** to further develop support and capacity for self-management.

3.3. Hospitals and specialist outpatient clinics

Secondary care specialists should ensure that prescribing records reconcile with individuals' current prescriptions and check what medicines individuals are taking, as it is known that prescribing discrepancies can occur between primary and secondary care records.[70-72] Where appropriate specialists should access, check and update current prescribing information from individual's Emergency Care Summary.

Secondary care should establish and communicate changes in antidepressant prescriptions started in the hospital stating intended treatment duration, or where a drug has been reduced or stopped the rationale for the prescribers actions.

3.4. General practice clusters

Engage with local Prescribing Support Teams, who have a wealth of experience improving the quality of prescribing through the use of local and national measures, datasets and tools.

4. Which groups of people should be targeted for review?

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This may vary depending on practice populations and prescriber preferences, however, we would advise that the following groups should be considered for review.

Table 1, Potential groups of people that receive antidepressants and may benefit from being prioritised for a regular proactive medicines review

- People receiving the same antidepressant continuously, long-term (≥2 years)

- Older adults (≥65 years) and/or frail adults
  - Receiving a SSRI plus antiplatelet/NSAIDs/DOAC/warfarin without gastro-protection, due to the increased risk of gastric bleed with this combination.
  - Receiving >1 defined daily dose per day of citalopram (>20mg per day) or escitalopram (>10mg per day) due to QTc prolongation.
  - Diagnosed with dementia, as antidepressants may provide limited antidepressant effects.
  - Receiving TCAs and other anticholinergics – reduce the anticholinergic drug burden, to reduce the risk of falls and confusion.

- People receiving combinations:
  - Antidepressant plus long-term (≥8 weeks) benzodiazepines and/or z-hypnotics (B-Zs)
    - B-Zs are associated with an increased risk of depressive symptoms, paradoxically worsen anxiety, and reducing the effectiveness of psychological treatments. Reviewing reducing B-Z use prior to assessing antidepressant need may be appropriate.
    - B-Zs prescribing and use is associated with the use of higher doses of SSRIs
  - Combination antidepressant treatment e.g. mirtazapine with SSRI/SNRI. There is a lack of evidence demonstrating the efficacy of this combination to treat depression. People initiated on combinations by psychiatry should be reviewed by specialist services.
  - Higher risk of QTc prolongation combinations:
    - Citalopram or escitalopram or TCAs plus: methadone, antipsychotics, antinausea, quinine, etc

- People receiving high dose SSRIs for the treatment of depression.

- People receiving low dose mirtazapine or trazodone: for insomnia or subtherapeutic doses of mirtazapine (<30mg per day) for the treatment of depression.

DOAC: direct oral anticoagulant. NSAID: non-steroidal anti-inflammatory drug. SSRI: selective serotonin re-uptake inhibitor. TCA: Tricyclic antidepressant
QTc prolongation see end of Section 2.5 for more information [link]

4.1. People receiving the same antidepressant long-term, for ≥2 years.

As already acknowledged this is a growing population;[1,2] they are less likely to have their antidepressant reviewed than people who have recently been initiated on treatment or are receiving a shorter course e.g. six months of treatment for the first episode of depression.[3,4] We also know that reviewing this group can result in 1 in 4 people having a change in treatment and some individual's reducing and/or stopping their antidepressant.[13]

4.2. Frail and older adults: avoidable adverse drug events, dementia and polypharmacy

All antidepressants are associated with increasing the risk of falls in the elderly.[38] SSRIs are also associated with an increased risk of gastrointestinal bleed, which is further increased when they are used in combination with antiplatelets, non-steroidal anti-inflammatory drugs (NSAIDs), direct oral anticoagulants (DOAC), and/or warfarin.[73-76] Therefore proactively reviewing people in this group will help to ensure appropriate use and help minimise avoidable adverse drug events and harms, although for some individual's it may mean initiating appropriate gastro-protection such as proton pump inhibitors as advised in local and national guidelines.[20,56]

Higher doses of citalopram and escitalopram are associated with an increased risk of QTc prolongation, therefore as per previous safety advice and current licensing restrictions all older adults (>65 years) that are receiving prescriptions for more than citalopram 20mg or escitalopram 10mg daily should be reviewed and considered for dose reduction and/or cessation where appropriate.[77] Where it is considered clinically appropriate, or people refuse to reduce their citalopram or escitalopram dose, discuss and document the risk of harm, and arrange regular cardiac QTc monitoring as per Table 2. Especially as older and/or frail adults are at higher risk of QTc prolongation which is associated with ventricular tachycardia and sudden cardiac death,[46] in part this due to ageing but can be exacerbated by comorbidities and multiple medicines e.g. antibiotics, cardiac, diuretic, psychotropics, respiratory, etc, and is important as older adults have more comorbidities and associated polypharmacy.[5] Therefore proactively reviewing polypharmacy will also help to reduce the risk of QTc prolongation and sudden death.

Table 2. Monitoring criteria for citalopram and escitalopram.[77]

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

Dementia: Antidepressants demonstrate limited benefits in treating depression in people with dementia,[15,78-80] for some individual's however they may reduce depressive symptoms and improve general functioning.[81] Although there are relatively few studies of antidepressants for the treatment of agitation and psychosis in dementia sertraline, citalopram and trazodone have been used and are associated with modest reductions in symptoms of agitation and psychosis.[82,83]

Polypharmacy and anticholinergic effects: TCAs commonly cause anticholinergic effects, as do other medicines therefore please consider TCA use in relation to other prescribed and non-prescribed medicines with anticholinergic effects such as antihistamines, anti-Parkinson's medicines, urinary antispasmodics, some antinausea medicines, etc. [see Polypharmacy guidance for more information]. These anticholinergic effects are associated with an increased risk of dry mouth, blurred vision, cognitive dysfunction, urinary retention, falls, etc.[28]

4.3. People receiving antidepressants in combination with other psychotropics

Benzodiazepines and/or z-hypnotics (B-Z) are sometimes started to treat anxiety and/or insomnia symptoms prior to starting an antidepressant for depression or anxiety, or to treat agitation, anxiety or insomnia symptoms associated with starting an SSRI.[20,56] In some cases, as with all B-Z use, this has led to long-term (≥4 weeks) regular B-Z use sometimes lasting for years.[84] Conversely, some B-Zs may have been initiated to treat avoidable adverse drug effects such as insomnia and/or agitation caused by higher SSRIs doses,[35,36] or associated with signs and symptoms of poorly controlled depression, anxiety or back pain. However B-Zs only demonstrate marginal benefits for short-term relief of insomnia and some anxiety

disorders, and as already acknowledged can result in long-term chronic use which is contrary to good practice, guidance, and terms of the license.[28,63] Such B-Z use is known to worsen depressive symptoms, cause cognitive dysfunction and other avoidable adverse effects, and reduce the efficacy of some psychological therapies.[84-87] Therefore this should be considered one of the priority groups for review. Firstly the long-term B-Z drug should be reviewed and gradually withdrawn where appropriate using an agreed structured and planned reduction schedule, although a small minority of individuals may require longer-term B-Z treatment with regular review to optimise care and minimise street B-Z use, see benzodiazepine and z-hypnotic quality prescribing advice for more detail [link].

Using more than one antidepressant is not recommended, unless it is on the advice of an individual's regular consultant psychiatrists for the treatment of treatment resistant depression, for example. The evidence however, supporting the use of such combinations is poor, although antidepressant augmentation with an antipsychotic or lithium can be more effective; providing clearer benefits, but these are not without their risks and require extra monitoring which is often lacking.[20,88,89]

Combining an SSRI or serotonin and noradrenaline re-uptake inhibitors (SNRIs) such as venlafaxine with mirtazapine is a strategy that is sometimes used by some specialist services, such prescribing can and does influence general practitioners prescribing.[4] However, non-specialist psychiatry prescribers should not initiate such antidepressant combinations unless it is on the advice of specialist services as the potential benefits of such combinations are small, and may be of questionable clinical value due to the variable response rates – from marginal benefits in observational studies to no difference in randomised placebo controlled studies.[20,90,91] Another feature of SSRI/SNRI plus mirtazapine combination is the routine use of low dose mirtazapine 15mg daily; sometimes it is added for its short-term sedating antihistamine effects (also seen with trazodone). In part, these additional antidepressants are possibly being used to treat SSRI/SNRI induced insomnia, agitation etc., and as an alternative to B-Z; however, this combination is of questionable benefit, and it may be more appropriate to reduce the dose of the SSRI/SNRI to minimise potential adverse effects and drug-related harms rather than adding extra psychotropics, especially as tolerance can quickly develop to mirtazapine and trazodone's sedating effects.[69,92]

Neuropathic pain plus depression/anxiety treatment may require treatment with two antidepressants e.g. TCA for neuropathic pain and an antidepressant for depression, such combination may be appropriate to reduce symptoms (not two TCAs). However, use should be reviewed regularly, considering interactions, adverse and synergistic effects, e.g. TCA dose related QTc prolongation (higher doses greater risk of prolongation),[93] sedating effects, etc. There are risks in switching from a TCA and an effective antidepressant (for depression for example) to a TCA or duloxetine to treat both pain and mood, that the TCA or duloxetine may only be effective for one condition, and not the other. Individuals may not tolerate higher doses of TCAs or duloxetine which can be more effective for treating depression.[20,35,48,49]

QTc prolongation, as outlined above, can also be increased with the co-prescribing of a range of medicines. A list of medications known to prolong the QT interval can

be found on the Credible Meds website [link]. This is an American website that categorises drugs based on their risk. It is recommended that you check the lists for drugs commonly used in your area of practice to familiarise yourself with the risks. This site requires registration in order to gain access to the lists (registration is free). It is advised that you set up registration and become familiar with the site. Alternatively, you can access a table from Stockley's Drug Interactions [link].[94]

4.4. High dose SSRIs for the treatment of depression

Over the years prescribers have been heavily criticised for prescribing subtherapeutic licensed[d] doses of TCAs for the treatment of depression.[95,96] While TCAs and SNRIs demonstrate dose-response effects, with larger doses being more effective for depression treatment,[35,36,48] higher than standard daily doses of SSRIs: 20mg citalopram/fluoxetine/paroxetine, 50mg sertraline or 10mg escitalopram, do not provide better response rates[e]. Not even for poor or partial responders.[35-37,39] Standard SSRI doses provide the optimal balance between efficacy and minimising adverse effects and harms, due to their flat dose-response curve for the treatment of depression, meaning that '20's plenty and 50's enough' – of standard doses – to provide the full antidepressant effect.

While a range of depression campaigns and most depression guidelines, nationally and internationally, have heavily promoted the message 'to increase the dose' for all classes of antidepressants for poor and non-responder,[56,97-99] a minority of guidelines have highlighted the differences in response and efficacy between SSRIs and other antidepressants.[20,100] Individuals and prescribers however also have greater expectations that higher doses are more effective for routine treatment of depression,[4,8] in part this may be due to guidelines, training and the broad message 'to increase the dose', as well as individuals and/or societal expectations and beliefs regarding medicines.[26,101,102]

In 2011, in the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) issued advice regarding new maximum daily dose restrictions, contraindications, and warnings for citalopram and escitalopram use.[77] Health Boards issued local advice on reviewing citalopram/escitalopram doses: reviewing, reducing doses and if necessary switching to an alternative antidepressant where appropriate.[103] Anecdotally from prescribers' and general practice feedback, of those individuals that were reviewed: some stopped, some required a switch to an alternative antidepressant; while the vast majority that were required to continue treatment were continued on lower doses as per MHRA advice without worsening their depressive symptoms.

[d] Licensed dose: Is the approved dose or dose range that medicines are licensed to be prescribed at by the regulatory authority – Medicines and Health Care products Regulatory Agency – for the condition that they approved to treat, e.g. sertraline for depression treatment has a dose range of 50mg to 200mg per day.
[e] Higher SSRI doses can be more effective for treating some anxiety disorders such as OCD.63

4.5. Low dose mirtazapine and trazodone for sedation

As already acknowledge (see section 3.3) low daily doses of mirtazapine 15mg or trazodone 100mg or less, are commonly used to treat insomnia and anxiety symptoms, due to their sedating antihistamine effects.[69,92] However, people commonly develop tolerance to such effects and therefore longer-term use – as with B-Z drugs – maybe inappropriate, especially as tolerance usually develops within a couple of weeks to these sedating effects.

Low dose mirtazapine is also subtherapeutic for the treatment of depression.[36,69] If pharmacological treatment is considered appropriate and necessary then the dose should be increased within a couple of days to a therapeutic dose of 30mg per day, with an agreed plan for follow up within 2-4 weeks to assess efficacy and tolerance.

5. The 7-Steps medication review

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Domain	Steps	Process
Aims	1. What matters to the patient?	**Review diagnoses and identify therapeutic objectives with respect to:** • What matters to me (the patient)? • Understanding of objectives and limitations of drug therapy • Management of existing health problems • Prevention of future health problems
Need	2. Identify essential drug therapy	**Identify essential drugs (not to be stopped without specialist advice):** • Drugs that have essential replacement functions (e.g. levothyroxine) • Drugs to prevent rapid symptomatic decline (e.g. heart failure, relapse of depression).
	3. Does the patient take unnecessary drug therapy?	**Identify and review the (continued) need for drugs:** • Have non-pharmacological approaches been considered/used • With temporary indications e.g. first episode of depression treated for 6 months and course complete, consider managed reduction and stop. • With higher than usual maintenance doses e.g. SSRI greater than 20's plenty or 50's enough for depression. • With limited benefit in general for the indication they are used for e.g. co-prescribed benzodiazepine or z-hypnotic with antidepressant • With limited benefit in the patient under review
Effectiveness	4. Are therapeutic objectives being achieved?	**Identify the need for adding/intensifying drug therapy in order to achieve therapeutic objectives:** • To achieve symptom control/clinical targets • To prevent disease progression/exacerbation
Safety	5. Does the patient have ADR/Side Effects or is at risk of ADRs/Side Effects? Does the patient know what to do if they're ill?	**Identify patient safety risks by checking for:** • Drug-disease interactions • Drug-drug interactions (see *Cumulative Toxicity* tool) • Robustness of monitoring mechanisms for high-risk drugs • Drug-drug and drug-disease interactions • Risk of accidental overdosing (Yellow Card Scheme) **Identify adverse drug effects and harms by checking for** • Specific symptoms e.g. insomnia, agitation, dry mouth, etc. • Cumulative adverse drug effects/harms (see *Cumulative Toxicity* tool) • Drugs that may be used to treat adverse drug effects/harms caused by other drugs e.g. benzodiazepine or z-hypnotic for insomnia
Cost-effectiveness	6. Is drug therapy cost-effective?	**Identify unnecessarily costly drug therapy by:** • Consider more cost-effective alternatives (but balance against effectiveness, safety, convenience)

Patient centeredness	7.	Is the patient willing and able to take drug therapy as intended?	**Does the patient understand the outcomes of the review?** • Does the patient understand why they need to take their medication? • Consider Teach back **Ensure drug therapy changes are tailored to patient preferences** • Is the medication in a form the patient can take? • Is the dosing schedule convenient? • Consider what assistance the patient might have and when this is available • Is the patient able to take medicines as intended? **Agree and Communicate Plan** • Discuss with the patient/carer/welfare proxy therapeutic objectives and treatment priorities • Decide with the patient/carer/welfare proxies what medicines have an effect of sufficient magnitude to consider continuation or discontinuation • Inform relevant healthcare and social care carers change in treatments across the care interfaces Add the READ code **8B31B** to the individuals record so that it is clear their medication has been reviewed

6. Reducing and stopping antidepressants

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- Standard reduction: SSRI, SNRI, TCA, Other antidepressants
- Difficulty withdrawing SSRI/SNRI
- Significant difficulty/fear of withdrawing SSRI/SNRI

6.1 Discontinuation

All classes of antidepressants can cause discontinuation/withdrawal symptoms, especially when stopped abruptly. Therefore, this advice is intended to provide prescribers and individuals with a range of options to appropriately support and enable successful antidepressant reduction and discontinuation.

Discontinuation/withdrawal effects may also occur to a lesser extent when doses are missed or reduced. It is however, unknown and debatable what the specific incidence and prevalence is – as this can vary by individual antidepressant (e.g. more commonly occurs with paroxetine and venlafaxine), duration of treatment, the condition being treated and study design – studies have indicated that that up to 12% of people receiving placebo and up to 32-56% of people receiving different antidepressants may be affected.[104-106] Although some individuals may be more sensitive to withdrawals than others, and unfortunately, it is difficult to know who will or will not experience discontinuation/withdrawal effects.

The term ‘discontinuation symptoms’ is used to describe symptoms experienced on stopping medicines that are not drugs of dependence, although there are important semantic differences in the terms ‘discontinuation’ and ‘withdrawal’ symptoms – the latter implying addiction, the former does not.[15] While the distinction is important for precise medical terminology, it is irrelevant when it comes to personal experiences and how an individual may describe their signs and symptoms.

The optimum rate of taper to prevent withdrawal effects is unknown.[17,18] Therefore, the prescriber and individual should discuss and agree on the most appropriate approach to reducing the dose and reviewing progress – for some this will mean ‘low and slow reductions’. This will vary depending on individual’s needs, circumstances, age, clinical condition, other comorbidities being treated, as well as the duration of antidepressant treatment. However, some individuals who stop antidepressant treatment for depression may experience a depressive relapse. A recent large robust trial by Lewis et al.[107] assessed the risk of relapse for people who indicated that they were ready to stop their antidepressant which they had taken for 2 years or more. During 52 week follow up period 39% of people continuing antidepressant treatment experienced a depressive relapse, and 56% of those discontinuing treatment; 39% of whom restarted antidepressant treatment.

6.2 Considerations for reduction and/or stopping

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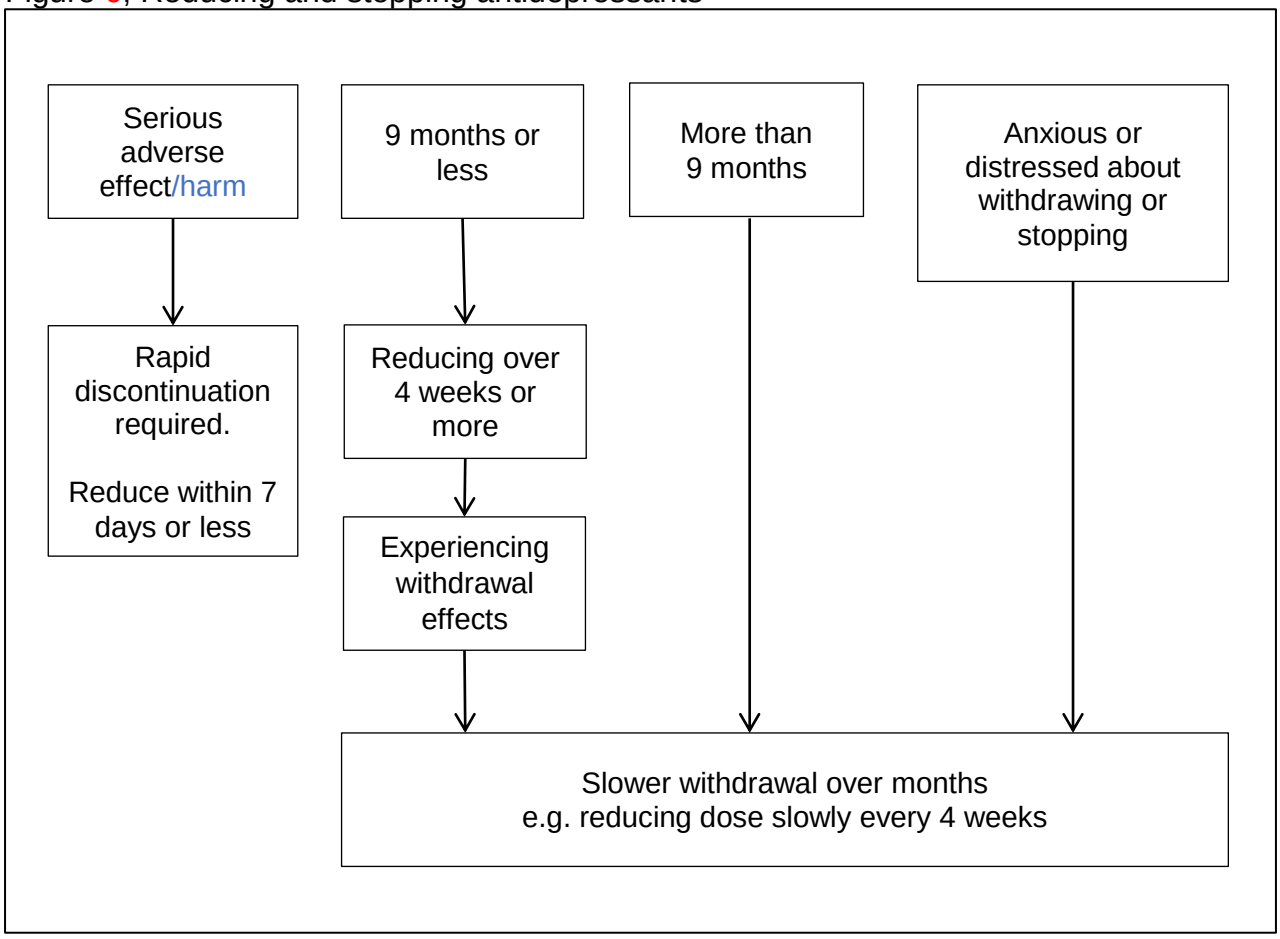
Figure 6, Reducing and stopping antidepressants



The strategy for reducing/stopping antidepressants should be guided and informed by the individual's preferences and needs. Consider the clinical situation when reviewing and discussing reducing/stopping antidepressants. Encourage individuals' to discuss stopping their antidepressants with their prescriber before doing so. By discussing and planning withdrawals, the most appropriate rate of reduction can be agreed and planned with the individual according to their preferences and needs:

- Experiencing serious adverse effects/harms; may require rapid discontinuation within 7 days or less (Table 3).
- Completed a 9 month[f] or less course of antidepressant treatment e.g. first episode of moderate to severe depression – reduce over a minimum of 4 weeks, but some individuals may need a slower reduction.
- Completed a longer course (9 months or more) of antidepressant treatment, and/or a history of recurrent depression or anxiety. Reducing and tapering the dose at a slower rate over months may be more appropriate.

[f] Shorter courses of antidepressant treatment may be less likely to be associated with discontinuation/withdrawal effects. However the rate of reduction should be guided by individual's preferences and needs.

- Anxious about reducing/withdrawing antidepressants or history of experiencing discontinuation effects. Reducing and tapering the dose at a slower rate over months may be more appropriate.

Where people experience significant or unbearable withdrawal effects, increasing back to the previous dose that did not cause withdrawals, and stabilising, and then considering a slower rate of reduction may help.

Table 3. Serious adverse effects/harms which may require rapid discontinuation

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

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

6.2.1 Assess the individual's readiness to reduce and/or stop

It is important that an individual's motivation and readiness for reductions and/or discontinuation is adequately assessed, and where appropriate and agreed tailored dose reductions are planned and where implemented, regularly reviewed. Signposting/referral for interventions to support changes to prescribing including psychosocial/logical interventions should also be considered.

What is the risk-benefit balance of continuing current antidepressants and doses? For example, anticholinergic effects versus neuropathic pain control, or is it reducing the signs and symptoms of the condition it was prescribed for, or does the antidepressant need to be stopped due to other increased risks such as cardiovascular disease, QTc prolongation risk or a newly diagnosed condition.

Has the individual completed the planned and agreed course or trial of treatment? For example in relation to depression, is the individual experiencing residual symptoms such as sleep issues, irritability and ruminating, motivation (have they managed to do something they like to do) and do they have plans for the future

(moving on from depressive episode). These factors may indicate that an individual is suitable to consider reducing and stopping their antidepressant after completing an appropriate course of treatment e.g. 6 months for the first episode of depression, or 12 or 24 months of treatment depending on the number of depressive episodes and relapses.

Discontinuation/withdrawal symptoms: These may begin on average within 2 days (up to 5 days) of stopping or occasionally after dose reduction or after missed doses; generally subsiding within 7-10 days,[15,20] but may include a wide range of symptoms which can vary in intensity and vary depending on which antidepressant is being stopped (Tables 4 and 5). However for the majority, these symptoms are usually mild and self-limiting, although a minority of people may experience severe or prolonged discontinuation/withdrawal symptoms e.g. flu-like, electric shocks (brain zaps), vivid dreams, dizziness, diarrhoea, etc. Unfortunately, the optimum rate of taper to prevent discontinuation/withdrawal symptoms is unknown.[17,18]

Table 4. Clinical presentation of discontinuation/withdrawal symptoms

	Symptoms
Systemic, cardiac effects	Flu-like symptoms*, **dizziness/drowsiness*,** tachycardia (fast heart rate)*, **impaired balance, fatigue,** weakness, **headache**, dyspnea (breathlessness)
Sensory	Paraesthesia (burning, pricking sensation)*, electric shock–like sensation (“brain zaps/body zaps”)*, sensory disorders, dysaesthesia (strange sensation e.g. burning, itching), itch, tinnitus, altered taste, blurred vision, visual changes
Neuromuscular	Muscle tension*, myalgia (muscle pain)*, neuralgia (nerve pain)*, agitation*, ataxia (lack of muscle co-ordination)*, tremor
Vasomotor	Perspiration*, flushing*, chills*, impaired temperature regulation
Gastrointestinal	Diarrhea*, abdominal pain*, anorexia, **nausea, vomiting**
Sexual	Premature ejaculation*, genital hypersensitivity*
Sleep	**Insomnia,** nightmares, vivid dreams, hypersomnia (excessive sleepiness)
Cognitive	Confusion*, disorientation*, amnesia*, reduced concentration
Affective	**Irritability,** anxiety, agitation, tension, panic, depressive mood, impulsivity, sudden crying, outbursts of anger, mania, increased drive, mood swings, increased suicidal thoughts, derealization, depersonalization
Psychotic	Visual and auditory hallucinations
Delirium	Typically only with tranylcypromine

Adapted from Henssler et al 2019.[104] Symptoms in bold occur more frequently. *serotonin related

Table 5. Antidepressant discontinuation/withdrawal symptoms

Antidepressant class	Most commonly associated[a]	Symptoms[b]	
		Common	Occasional
SSRI, Clomipramine (TCA)	Paroxetine	Flu-like symptoms (chills, myalgia, excess sweating, nausea, headache), 'shock like' sensations, dizziness exacerbated by movement, insomnia, excess (vivid) dreaming, irritability , crying spells	Movement disorders, concentration, memory difficulties
SNRIs	Venlafaxine	Same as above, due to serotonin effects	Same as above
TCAs	Amitriptyline, Imipramine	Flu-like symptoms, insomnia, excess dreaming. *Anticholinergic rebound* – more common in the elderly: headache, restlessness, diarrhoea, nausea and vomiting	Movement disorders, mania, cardiac arrhythmias.
Other	Mirtazapine[c]	Anxiety, panic attacks, insomnia, irritability, nausea	
	Agomelatine		No discontinuation symptoms have been reported[d]
	Trazodone		Rarely SSRI type withdrawals[e]
	Vortioxetine		No discontinuation symptoms have been reported[f]

a. Although most commonly associated with the listed medicines, other medicines in the group may cause similar symptoms.
b. Symptoms: As individuals may or may not experience discontinuation/withdrawal symptom, and the intensity and range of symptoms may vary by individual, people may experience or identify symptoms not listed above.
c. Limited data: mirtazapine case studies, see Cosci et al 2017.
d. Agomelatine and vortioxetine are rarely used. At time of writing no case reports in literature.
e. See Haddad et al 2001. and Otani et al 1994. for more detail.
f. Adapted from and informed by Maudsley and Psychotropic Drug Directory.

6.3 Standard reduction approaches

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

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

6.3.1 Selective serotonin re-uptake inhibitors (SSRI)

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

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

Steps: the rate of withdrawal will vary with individual's needs e.g. weekly to 4 weekly reductions for some.
All doses are single daily doses
*Alternate day dosing 40mg/20mg
**Alternate day dosing with 20mg capsule, or consider using fluoxetine liquid
***Alternate day dosing with 50mg tablet
† Some individual's may require to be switched to an alternative SSRI if experiencing significant withdrawals, see below.

6.3.2 Serotonin and noradrenaline re-uptake inhibitors (SNRI)

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Most individuals will be able to slowly withdraw and discontinue duloxetine and venlafaxine without any adverse effects. Where individuals experience discontinuation/withdrawal effects after stopping, it may be appropriate to restart the antidepressant at the previous dose and frequency for 7 days then switch to a long acting SSRI, interactions and contra-indications allowing (section 6.4).

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

Steps: the rate of withdrawal will vary with individual's needs e.g. weekly to 4 weekly reductions for some, or longer and slower reductions for others.

Note: Venlafaxine 300mg daily used as example, as individuals on higher doses are usually under the care of community mental health teams who should be involved in decisions to reduce or withdraw.

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

6.3.3 Tricyclic antidepressants (TCAs)

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

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

a. The same reduction schedule would be advised for:

Clomipramine	Dosulepin (dotheipin)	Doxepin
Imipramine	Nortriptyline	Trimipramine

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

6.3.4 Other antidepressants and monoamine oxidase inhibitors (MAOIs)

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

Steps: the rate of withdrawal will vary with individual's needs e.g. weekly to 4 weekly reductions for some.

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

6.4 Difficulty withdrawing SSRI/SNRI or fearful

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

Convert to long-acting SSRI, then reduce and stop

Reduce the total daily dose in a stepwise fashion to: paroxetine 20mg, venlafaxine 75mg, duloxetine 30mg daily (see 6.3.1 SSRI and 6.3.2 SNRI). Then convert to an approximate dose equivalent* of fluoxetine, citalopram or sertraline (Step 1), using standard capsules, tablets or liquid, and stabilise on that dose for 3-7 days then stop. Some individuals may prefer or need slower reductions.

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

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

Steps: the rate of withdrawal will vary with individual's needs e.g. weekly to 4 weekly reductions for some.

* Approximate dose equivalents

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

***Approximate dose equivalents and switching considerations:**

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

Fluoxetine liquid may be required for a few individuals that require or prefer a slower reduction at weekly to 4 weekly intervals.

6.5 Significant difficulty or fears withdrawing SSRI/SNRI

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For a very small minority of individuals, slower graduated reduction may be appropriate:

- Where standard reduction (6.3.1 SSRI or 6.3.2 SNRI) and/or
- Difficulty discontinuing/withdrawing SSRI/SNRI (Section 6.4) have been unsuccessful.

This approach will help flatten the reductions in plasma drug concentrations at lower doses (Figure 7)

First, reduce current antidepressant to standard dose as per 6.3.1 SSRI or 6.3.2 SNRI. Then convert to an approximate dose equivalent of fluoxetine 20mg/5ml liquid.

Fluoxetine 20mg is approximately dose equivalent* to:

- Citalopram 20mg
- Escitalopram 10mg
- Fluvoxamine 50mg
- Paroxetine 20mg
- Sertraline 50mg
- Duloxetine 30mg
- Venlafaxine 75mg

***Approximate dose equivalents and switching considerations:**

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

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

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

Note:

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

Figure 7, Fluoxetine hyperbolic dose reduction

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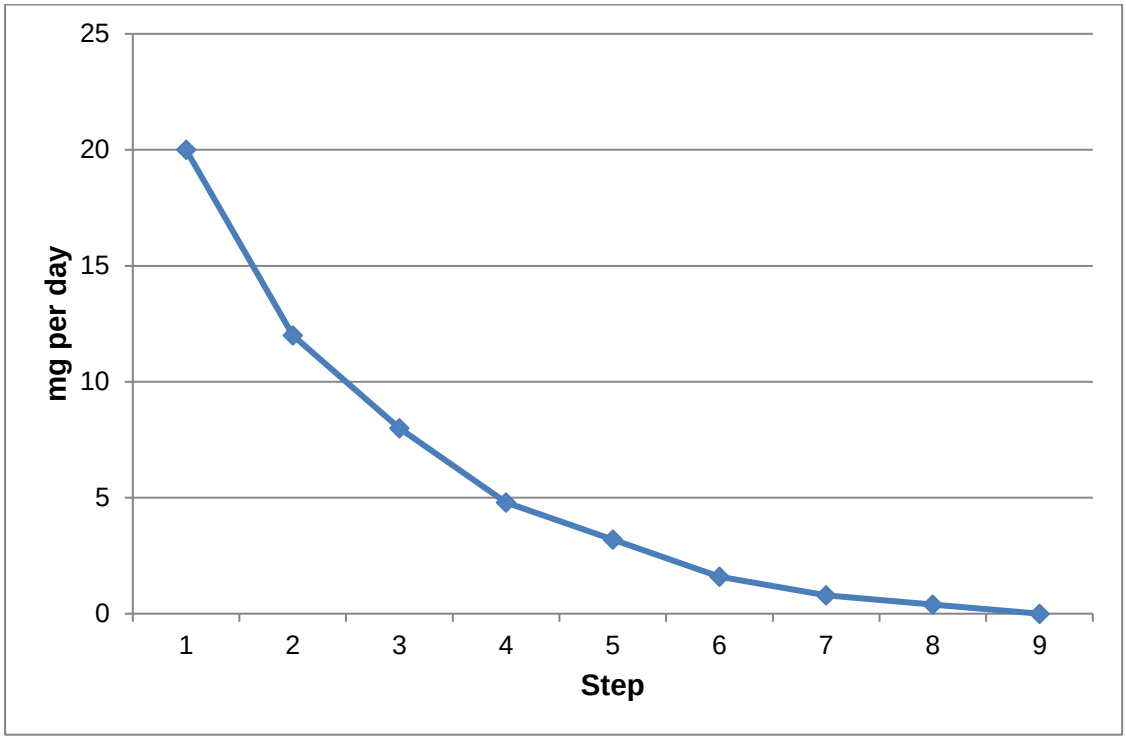

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7. Examples from practice and case studies

Lived Experience 1

I am learning that my experience of psychiatric drug prescribing is not an unusual one. In May 2013, I suffered a two-week period of insomnia due to work related stress, and visited my GP. I was prescribed mirtazapine, an antidepressant. Unfortunately I had a bad reaction to the drug; very increased anxiety within one week, and suicidal thinking within two weeks. I was then prescribed antipsychotics and a benzodiazepine. The benzodiazepine helped with the anxiety, but provided short lived relief, and I realised it was possibly an addictive medicine which I then tried to avoid.

The anxiety remained, I had no relief. I was then prescribed imipramine, a tricyclic antidepressant, and told I should slowly increase the dose over 6 weeks when the relief would begin to be felt. After 6 weeks there was no improvement. My GP told me that I needed to 'believe in the antidepressant and then it would work'. At this point I began to descend into severe depression.

During periods depression, the anxiety would lessen, but as the depression eased the anxiety would return – like two sides of the same coin. With no relief from the drugs, I experienced multiple admissions to different mental hospitals over a number of months. First to a mental hospital, where different drug combinations were tried. Then another where a further ten different psychiatric drugs were tried. Then finally two admissions to the same hospital, as a precaution to prevent suicide attempts. During these two admissions I was given 15 courses of Electro Convulsive Treatment (ECT). These treatments did not work either. There would be a day of hyperactivity and then a plunge back into even deeper depression. I volunteered to stop all ECT treatments. My Hamilton Depression rating was frequently close to the maximum of 45. I was very seriously ill, and the psychiatrist at that time diagnosed me as chronic treatment resistant bi-polar depressed, and promptly put me onto lithium. Before long I was having trouble with shaking hands, acute nervous agitation and unbearable anxiety.

Every day was a struggle to survive. My mind was constantly occupied with ways to kill myself and there were many attempts, which very luckily were not successful. Only time spent with the excellent nurses and other individuals in the hospital garden eased my suffering and despair.

Eight years later, I am fully recovered. How did this happen? I was very lucky to have had psychotherapists visit me every day, and talking therapy with a psychotherapist in the health centre once a week. These talking sessions kept me alive. After three and a half years of being prescribed psychiatric drugs all descriptions, my psychiatrist referred me to a brilliant psychologist. Talking with her helped to keep me alive.

But finally, it was clear to me that the only thing we had not tried was coming off all psychiatric drugs. My psychiatrist eventually agreed to help me do this. Within 8 weeks, on a slow reducing dose I was lifted out of depression for the first time in four years.

Three months later I was allowed to stop the last drugs. I have never taken a single pill of any description ever since. While coming off the drugs, I started low sugar, low carbohydrate, high fibre diet with some minerals and vitamins to build up my immune system. I lost 3 stone of weight that had accumulated on the antidepressants, and restored my physical health as well as my mental health. Before reducing the psychiatric drugs, my wife had enrolled me into an art group. Although I was severely depressed at the time, the simple act of joining a group of people who enjoyed art had a great positive effect on me; I began to enjoy learning to be better at drawing and painting. I found myself looking back at previous art work and being amazed that I had actually achieved something. My wife also enrolled me in the volunteers gardening group where I enjoyed meeting others in the public garden where we would do small jobs that gave us all a sense of achievement and belonging. I then joined a choir. The atmosphere was always friendly and I began, very slowly, to begin to look forward. My mind was slowly shifting from endless rumination towards normal thought processes of linear continuity. Finally, Thai Chi and weekly walks with the local walking club all helped me to recover full health.

Lived Experience 2

In 2014, my GP prescribed sertraline to help alleviate my anxiety. Following a traumatic experience, and an operation, I was petrified of being left by myself. I was started on 50mg a day which, after an assessment by Psychiatry, was stepped up to 200 mg over the course of four months. At the same time, I attended a six-week group CBT course through Primary Care Mental Health services and started receiving regular counselling. Concurrently, I was seen and assessed by cardiology, gastroenterology and genetics which ultimately compounded my anxiety and increased the medicine burden to around 20 tablets a day.

Fast forward to August 2021 and I remain on the same daily dose. I am subject to annual medicines reviews by my GP where the question of lowering the dose is discussed. The first time I panicked, as I hadn't even considered it, so naturally any adjustment was put on hold. I have never felt pressurised or been made to feel guilty for 'failing to cut back'. I have a supportive GP who understands I have no desire to ever feel the way I did before I started taking antidepressants. I have done behavioural therapy and learned the tools to change my way of thinking, but for me there has always been a huge physical element to my anxiety, they called it 'Double Anxiety' at the time. Add to that the physical health problems, additional drugs, and changes in my personal circumstances. So far, the time has never been right to start cutting back. When the time is right, however, I know I have a GP who is mindful of my reservations and who will let me go at my own pace.

NHS Greater Glasgow and Clyde.[13]

GPs were asked to proactively review a proportion of their practice patients prescribed the same antidepressant continuously long-term (≥2 years), as current guidelines advise up to 2 years treatment for some individual's with depression. Amitriptyline was excluded as it is more commonly used to treat neuropathic pain. Prescribing support pharmacists and technicians created the opportunity for proactive reviews by identifying potential patients for review, using data extraction tools enabling >150 hour audits to be completed within 2-4 hours, November 2009 to March 2010. The GPs then decided which of their patients to review.

78 of 96 practices participated. 8.6% (33,312/388,656) of all registered patients were prescribed an antidepressant, 47.1% (15,689) were defined as long-term users and 2,849 (18%) were reviewed. 811 (28.5%) patients reviewed had a change in antidepressant therapy: 7% stopped, 13% reduced dose, 5% increased dose, and 3% changed antidepressant, resulting in 9.5% (95% CI = 9.1% to 9.8% P<0.001) reduction in prescribed daily dose and 8.1% reduction in prescribing costs. 6% were referred onwards, half to NHS Mental Health Services. Pre-review SSRI doses were 10–30% higher than previously reported.

Since 2009, this initiative has continued as a local prescribing initiative, enabling more than 8,000 people in more than 180 general practices to be reviewed between 2009/10 and 2014/15. However this represents less than 2% (8,000/451,084) of people receiving long-term treatment[g], and lacked long-term follow up to assess relapse and recurrence rates.

Strength: Enable GPs to proactively review their own patients, enabling more people to be reviewed in a short period of time. Demonstrates use of electronic systems in enabling appropriate people to be identified and called for review. Demonstrates the effectiveness of pharmacy general practice teams in supporting and facilitating proactive GP reviews.

Limitations: Prescribers were asked to use their own clinical judgement for reviewing and reducing antidepressants, however they did not have structured advice as outlined in this guideline which may help overcome some of the barriers outlined in 2.3 above. Limited numbers of people reviewed. Limited resources and long-term follow up to assess longer-term impact.

[g] Estimate calculated from: previous studies indicate approximately 50% of people receive long-term treatment.13,108 Current Medicines use in Mental Health indicates that 902,168 people received antidepressants in 2017/18. Therefore approximately 451,084 people are receiving long-term treatment in Scotland.

NHS Highland[109]

A 12-month pilot service was implemented in two general practices in remote and rural Scotland. Patients were referred by general practitioners to specialist mental health pharmacist independent prescribers. The objective of this work was to pilot and evaluate this service development from the perspectives of the patients and the care team. The pharmacists routinely recorded patient-specific data of all clinical issues, actions at the time of each consultation, and patient outcomes. Outcomes were assessed using baseline and follow-up Patient Health Questionnaire (PHQ-9) and/or Generalised Anxiety Disorder (GAD-7) rating scales, a patient survey and interviews with members of the primary care team (2 pharmacists, 2 psychiatrists, 3 GPs and a general practice manager).

84% (75/89) patients referred attended their first consultation; 63% (n=47) had a diagnosis of mixed depression and anxiety, 29% (n=22) depression. There were 324 consultations (median 3, IQR 2–5, range 1–14) and 181 prescribing actions; involving increasing dose (43%, n=77), or starting antidepressants or other medicines (33%, n=59). Unfortunately 21% (n=16) of patients did not attend their appointment and were lost to follow up, however at pilot completion 45% (n=34) patients had PHQ-9 and/or GAD-7 scores reduced by 50%. Two patients stopped their antidepressant.

70 patients were invited to participate in the questionnaire (5 were excluded as 3 had left the practice and 2 terminally ill). 21% (n=15) completed and returned responses, which were overwhelmingly positive with the majority (93%) of respondents strongly agreeing that they would recommending consulting a pharmacist to others. Patients stated that they ‘felt more at ease’, that the pharmacist ‘took time to get to know me’, ‘really listened’ and they ‘immediately felt comfortable’.

Staff interviews identified three key themes integration, enablers and barriers. There was a willingness of practice staff to embrace service redesign and integrate the pharmacists within the general practice team. The change aligned to the new GP contact in Scotland, and was accepted by patients, ‘they [patients] were on board quite quickly as well…’. The work was perceived as not negatively impacting on GP workload, and was consider as being positive ‘I could see it being a positive that she [pharmacist] was able to prescribe.’ Barriers, were focused on the initial planning and clinic set up.

Strength: Reviewing patients in general practice. Creating capacity by taking work from GPs. Integrated well into general practice Demonstrates the potential support that specialist mental health clinical pharmacists can provide in general practice.

Limitation: Small number of people included over the 12 month period; limiting reach, considering that 1 in 5 adults in general practice receive antidepressants. Did not appear to up skill/support GPs to review their own patients. Low number of patients reduced/stopped, however it was unclear if people were referred at the start of treatment or after receiving long-term treatment.

Others

Maund et al, have completed a systematic review regarding published studies that focused on reviewing, reducing and stopping antidepressant.[18]

Of 15 included studies, 12 studies (8 randomized controlled trials, 2 single-arm trials, 2 retrospective cohort studies) were included in the synthesis. None were rated as having high risk for selection or detection bias. Two studies prompting primary care clinician discontinuation with antidepressant tapering guidance found 6% and 7% of patients discontinued, vs 8% for usual care. Six studies of psychological or psychiatric treatment plus tapering reported cessation rates of 40% to 95%. Two studies reported a higher risk of discontinuation symptoms with abrupt termination. At 2 years, risk of relapse/recurrence was lower with cognitive behavioural therapy plus taper vs clinical management plus taper (15% to 25% vs 35% to 80%: risk ratio = 0.34; 95% CI, 0.18-0.67; 2 studies). Relapse/recurrence rates were similar for mindfulness-based cognitive therapy with tapering and maintenance antidepressants (44% to 48% vs 47% to 60%; 2 studies).

Cognitive behavioural therapy or mindfulness-based cognitive therapy can help patients discontinue antidepressants without increasing the risk of relapse/recurrence, but are resource intensive.

Strength: Includes a range of studies with different methodologies and different populations. Highlights that a complex intervention with tapering and psychological support may be more effective.

Limitation: The variations in individual studies methodologies across different health care systems, and small sample numbers. Not always clear how long individuals had been receiving the antidepressant for ranging from 3 months to more 9 months, for the majority of studies..

Case study 1

Patient Details Age/sex/ Occupation

- 74 year old lady
- Retired

History of presenting complaint/ reason for review

- Falls – no dizziness or light headedness. Has experience a number of falls over the years. Main cause balance and mobility. Has been referred to falls team.
- At review –
    - Pains in feet. States that 'lack of feeling in feet possibly to do with plantar fasciitis'
    - Higher dose of sertraline (100mg daily) 'made no difference'. Depression resolved.
    - Sometimes forgets to take alendronate – due timing of dose

Current Medical History and Relevant Co Morbidities

- Osteoporosis – 1 years
- Fractured neck of femur (right). Total hip replacement – 2 years
- Depression – 3 years. Related to death of husband after long illness
- Plantar fasciitis – 4 years
- Acne rosacea
- High blood pressure – 5 years
- Chronic kidney disease stage 3 – 7 years
- Lower back and knee pain – chronic
- Dyspepsia – 8 years
- Cerebral lacunar infarct – 7 years

Current Medication and drug allergies (Drug History)

- Aspirin 75mg daily
- Alendronate 70mg once weekly – takes before breakfast
- Co-codamol 30/500 tablets 2 tablets up four times a day if needed
- Co-codamol 8/500 tablets 2 tablets up four times a day if needed
- Fludrocortisone 50mcg daily
- Movelat gel apply up to three times a day if needed
- Omeprazole 20mg day
- Senna 7.5mg, take two at night (last ordered 12 months ago)
- Sertraline 100mg daily (initiated 2 years ago after death of husband)
- Simvastatin 40mg at night
- Stexerol D_3 1000U tablets, one daily per day

Drug allergies: co-trimoxazole – nausea and vomiting

Lifestyle and Current Function (Psychosocial history) inc. alcohol/ smoking/ diet/ exercise etc

- Lives alone
- Supportive family and neighbors. Sees sister and brother regularly
- Ex-smoker
- Does not drink alcohol

- Walks with stick

"What matters to me" (Patient Ideas, Concerns and Expectations of treatment)

- Reducing frequency of falls

Results e.g biochemistry, other relevant investigations or monitoring

- U&Es, LFTS, bone profile, HbA1c and FBC – all within normal range. eGFR = 45ml/min over estimating renal function.
- Weight 65kg, Height 1.62. IBW 54.2kg. Estimate creatinine clearance 35ml/min (CKD G3b)
- DXA scan – 1 year ago – severe osteoporosis
- BP 143/91 sitting, 116/78 standing. No symptoms of postural BP drop.
- Pulse 74 bpm regular, regular.

Most recent consultations

- Fall in garden 1 week ago. Laceration to forehead. 6 stitches in situ. Wound closed and dry with large black scab. No signs of infection. 6 stitches removed, no issues. Care advice given. No dressing.

Domain	Steps		Process	Patient specific issues to address
Aims	1.	What matters to the patient problems	**Review diagnoses and identify therapeutic objectives with respect to:** • Identify objectives of drug therapy • Management of existing health problems. Prevention of future health	• Reduce frequency of falls • Where appropriate reduce/minimise prescribed medicines that may add to the risk of falls.
Need	2.	Identify essential drug therapy	**Identify essential drugs (not to be stopped without specialist advice)** • Drugs that have essential replacement functions (e.g. thyroxine) • Drugs to prevent rapid symptomatic decline (e.g. drugs for Parkinson's disease, heart failure)	• Stroke prevention medicines: simvastatin, aspirin, hypertension control. • Osteoporosis treatment: alendronate and stexerol • GI protection – aspirin + sertraline GI bleed risk. • Chronic pain control
	3.	Does the patient take unnecessary drug therapy?	**Identify and review the (continued) need for drugs** • What is medication for? • with temporary indications • with higher than usual maintenance doses • with limited benefit/evidence of its use in general • with limited benefit in the patient under review (see Drug efficacy & applicability (NNT) table)	• 1st episode depression after death of husband – lady states 'higher dose sertraline not made much difference'. Mood good. Sleep poor since retired. SSRIs and higher doses associated with increased risk of falls. Trial reduce every 4 weeks 100mg to 50mg to 25mg then stop. • Hypertensive while sitting. Previous stroke – stop fludrocortisone. • Osteoporosis – forgets to take alendronate. Advised take at 11am Fridays (2 hours before and after meals) • Senna not required – stop.
Effectiveness	4.	Are therapeutic 50bjective being achieved?	**Identify the need for adding/intensifying drug therapy in order to achieve therapeutic objectives** • to achieve symptom control • to achieve biochemical/clinical targets • to prevent disease progression/exacerbation • is there a more appropriate medication that would help achieve goals	• Depression resolved – trial stop sertraline • Forgetting to take alendronate • As required co-codamol using both strengths is effective – not causing drowsiness, constipation.
Safety				

	5.	Does the patient have ADR/ Side effects or is at risk of ADRs/ side effects? Does the patient know what to do if they're ill?	**Identify patient safety risks by checking for** • if the targets set for the individual appropriate ? • drug-disease interactions • drug-drug interactions (see ADR table) • monitoring mechanisms for high-risk drugs • risk of accidental overdosing **Identify adverse drug effects by checking for** • specific symptoms/laboratory markers (e.g. hypokalaemia) • cumulative adverse drug effects (see ADR table) • drugs that may be used to treat side effects caused by other drugs **Sick Day rule cards**	• Two strengths of co-codamol for knee and back pain. Paracetamol only ineffective. Takes 8/500 during day and 30/500 at night. Knows not to take both at same time. Uses sparingly. • Fludrocortisone increasing risk of high blood pressure – stop. • Omeprazole required to continue as GI bleed protection due to aspirin need for stroke prevention.
Cost-effectiveness	6.	Is drug therapy cost-effective ?	**Identify unnecessarily costly drug therapy by** • Consider more cost-effective alternatives (but balance against effectiveness, safety, convenience)	• No issues. Formulary preferred list medicines options being prescribed

Patient centeredness	7.	Is the patient willing and able to take drug therapy as intended ?	**Does the patient understand the outcomes of the review?** • Consider Teach back **Ensure drug therapy changes are tailored to patient preferences by** • Is the medication in a form the patient can take? • Is the dosing schedule convenient? • Consider what assistance the patient might have and when this is available • Is the patient able to take medicines as intended **Agree and communicate plan** • Discuss with the patient/carer/welfare proxy therapeutic objectives and treatment priorities • Decide with the patient/ carer/ welfare proxies what medicines have an effect of sufficient magnitude to consider continuation or discontinuation • Inform relevant healthcare and social care carers, changes in treatments across the care interfaces	**Agreed plan** • Osteoporosis – forgets to take alendronate. Advised take at 11am Fridays (2 hours before and after meals) • Plantar fasciitis – Refer for podiatry review • Understands and agrees to changes to medicines • Poor sleep since retired – uses sleep hygiene techniques: low caffeine intake, reads when has insomnia/night-time wakening • Has capacity and is very independent and capable of looking after her own medicines

Key Concepts in this case

Summaries key points here

- eGFR over estimating renal function. Although eGFR is routinely reported with U&Es it does not routinely reflect older adults' renal function therefore it may be prudent calculate individual's creatinine clearance – see BNF Prescribing in Renal Failure section.
- Minimise the number of unnecessary medicines.
- This lady was open to reducing/stopping her sertraline – stating the higher dose was ineffective. Slow reduction every 4 weeks was appropriate as she had been taking sertraline long-term (≥2 years).
- Fludrocortisone – increases blood pressure, and lady was borderline hypertensive with a previous history of stroke therefore fludrocortisone may have increased the risk of future strokes.
- Podiatry assessment not included in routine falls team review therefore referral was needed.

Case summary

Patient Details Age/sex/ Occupation

- 60 year old lady
- Works part-time

History of presenting complaint/ reason for review

- At review the lady tells you her mood is good and she asks if she can stop her antidepressant?

Current Medical History and Relevant Co Morbidities

- Mixed anxiety depression (first episode) after son died 4 years ago.

Current Medication and drug allergies (Drug History)

- Paroxetine 20mg daily, for approximately 2.5 years
- Temazepam 10mg nocte, for approximately 3 years (Does not over order)

Drug allergies:

- Nitrofurantoin – rash

Lifestyle and Current Function (Psychosocial history) inc. alcohol/ smoking/ diet/ exercise etc

- Lives alone,
- No alcohol
- Looks after grandson at holiday and term time to help support her daughter-in-law.
- Mood good.
- Good concentration, appetite and weight stable, sleeping well.
- Looking forward to the future and seeing her grandson growing up.
- Denies thoughts of suicide/deliberate self-harm.

"What matters to me" (Patient Ideas, Concerns and Expectations of treatment)

- Would like to stop antidepressant as has been taking a long time

Results e.g biochemistry, other relevant investigations or monitoring

- Nothing of significance

Most recent consultations

- Urinary tract infection six months previously

Domain	Steps		Process	Patient specific issues to address
Aims	1.	What matters to the patient problems	**Review diagnoses and identify therapeutic objectives with respect to:** • Identify objectives of drug therapy • Management of existing health problems. Prevention of future health	Reducing medicines 1. Reduce paroxetine 2. Gradually reduce temazepam prescribed long-term (>8 weeks) not indicated long-term. Then
Need	2.	Identify essential drug therapy	**Identify essential drugs (not to be stopped without specialist advice)** • Drugs that have essential replacement functions (e.g. thyroxine) • Drugs to prevent rapid symptomatic decline (e.g. drugs for Parkinson's disease, heart failure)	• None ○ Temazepam loses efficacy after 2-4 weeks. Licensed for a maximum of 4 weeks use. ○ Paroxetine completed the course
	3.	Does the patient take unnecessary drug therapy?	**Identify and review the (continued) need for drugs** • What is medication for? • with temporary indications • with higher than usual maintenance doses • with limited benefit/evidence of its use in general • with limited benefit in the patient under review (see Drug efficacy & applicability (NNT) table)	• Temazepam ○ Insomnia – related to bereavement – sleep improved. • Paroxetine ○ Completed 6 month course of treatment. Now in resolved.
Effectiveness	4.	Are therapeutic objectives being achieved?	**Identify the need for adding/intensifying drug therapy in order to achieve therapeutic objectives** • to achieve symptom control • to achieve biochemical/clinical targets • to prevent disease progression/exacerbation • is there a more appropriate medication that would help achieve goals	• Temazepam ○ Insomnia – sleep improved as depression appears to be in remission. • Paroxetine ○ Depression resolved
Safety	5.	Does the patient have ADR/ Side effects or is at risk of ADRs/	**Identify patient safety risks by checking for** • if the targets set for the individual appropriate ? • drug-disease interactions • drug-drug interactions (see ADR table)	• Temazepam – increased risk of cognitive effects, falls, lower mood, etc. • Paroxetine – GI bleed risk, emotional blunting, etc. Higher risk of withdrawals than with other antidepressants

		side effects?	• monitoring mechanisms for high-risk drugs • risk of accidental overdosing	
		Does the patient know what to do if they're ill?	**Identify adverse drug effects/harms by checking for** • specific symptoms/laboratory markers (e.g. hypokalaemia) • cumulative adverse drug effects (see ADR table) • drugs that may be used to treat side effects caused by other drugs **Sick Day rule cards**	Mood improved, appears to have resolved.
Cost-effectiveness	6.	Is drug therapy cost-effective?	**Identify unnecessarily costly drug therapy by** • Consider more cost-effective alternatives (but balance against effectiveness, safety, convenience)	Temazepam liquid significantly more expensive than tablets. Diazepam longer half-life and number of preparations available.
Patient centeredness	7.	Is the patient willing and able to take drug therapy as intended?	**Does the patient understand the outcomes of the review?** • Consider Teach back **Ensure drug therapy changes are tailored to patient preferences by** • Is the medication in a form the patient can take? • Is the dosing schedule convenient? • Consider what assistance the patient might have and when this is available • Is the patient able to take medicines as intended **Agree and communicate plan** • Discuss with the patient/carer/welfare proxy therapeutic objectives and treatment priorities • Decide with the patient/ carer/ welfare proxies what medicines have an effect of sufficient magnitude to consider continuation or discontinuation • Inform relevant healthcare and social care carers, changes in treatments across the care interfaces	Discuss and agree plan 1. Continue non-pharmacological approach to support recovery: exercise, hobbies, minimise social isolation, etc. 2. Temazepam to reduce and stop: due to lack of efficacy and risk of ADEs. a. Switch to diazepam 10mg at night and reduce by 1mg every 2-4 weeks. b. Alternative: Temazepam liquid reducing by 1mg (0.5ml) every 2-4 weeks. (liquid higher financial cost). 3. Paroxetine (after stopping temazepam) Options: a. Reduce to 10mg daily for 4 weeks then 5mg daily for 4 weeks then stop. b. If problematic withdrawal or apprehensive: i. Switch to equivalent dose of fluoxetine (20mg/5ml) liquid for 7 days, then reduce by 1ml (4mg) every 4 weeks.

Key Concepts in this case

Summaries key points here

- Benzodiazepines are associated with an increased risk of depression and are only licensed for a maximum of 4 weeks use. Stopping the temazepam is a priority due to increased risk of avoidable ADEs.
- Paroxetine is associated with withdrawals. Therefore have a range of options, and agree the most appropriate approach to reducing may improve the chances of successful withdrawal.

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Appendix 1. Sleep hygiene: Patient information leaflet

[Return to Main points]

Things to consider that can help and improve your quality of sleep and reduces anxiety.

- **How much caffeine do you take?** Remember that caffeine is a stimulant which is alerting and will affect your sleep quality and any anxiety. Common products that contain caffeine are tea, coffee, Irn-Bru, Cola, Red Bull, Proplus tablets and some energy drinks. Some pain medicines also contain caffeine Solpadeine, Propain, Panadol plus, Veganin etc. Therefore try to avoid all caffeine containing products after 6pm in the evening.

- **Alcohol** will affect the quality of your sleep, which may add to problems of anxiety and depression

- Other things that affect sleep
    - Watching television stimulates your brain with sound, light and motion. All of these stimulate your body and reduce fatigue.
    - Watching television in your bedroom. This can affect sleep quality as your body gets out of the habit of being trained to go to bed to sleep. Therefore remove TV from bedroom.
    - Noisy neighbours – difficult to deal with but ear plugs may help.

- How to improve sleep
    - **Establish a routine.** Go to bed and get up at the same time each day.
    - **No naps.** Try not to sleep during the day.
    - **Unwind the mind.** May help writing down problems and filing them away until the next morning. Address problems the next day, eg money/family problems.
    - **Take regular exercise**, such as a brisk 20 minute walk. Natural chemicals (endorphins) produced during exercise have a calming and relaxing affect after you have exercised. Do not exercise before going to bed or for 3 hours before going to bed as this can have the opposite effect.
    - Hot **caffeine free drinks** will warm you and help your body relax.
    - **Make time to relax.** Quiet time reflecting, listening to calming music such as classical, transient house, etc. 20-30 minutes a day would be enough. Watching TV does not help as it can be over stimulating.
    - Consider using ear plugs for noise that is affecting you which you cannot control.
    - If all else fails get out of bed and do something (read, etc) and then go back to bed.

Other information:

- NHS Inform: Sleep problems and insomnia self-help guide [link] https://www.nhsinform.scot/illnesses-and-conditions/mental-health/mental-health-self-help-guides/sleep-problems-and-insomnia-self-help-guide
- NHS How to get to sleep: Sleep and tiredness [link] https://www.nhs.uk/live-well/sleep-and-tiredness/how-to-get-to-sleep/
- The Sleep Charity: Adults [link]. https://thesleepcharity.org.uk/information-support/
- The Sleep Charity: Teen Sleep Hub [link] https://teensleephub.org.uk/

Appendix 2. Resources to support low intensity psychosocial and/or psychological interventions

The NHS Inform (Mental Health) website provides information regarding a range of mental health difficulties. In addition to self-help guides NHS Inform provides links to evidence based digital/online resources and telephone support based on CBT principles, see options below. Decisions regarding interventions should be based on an assessment of need and consider both suitability and acceptability for the individual[h]. Regular review is necessary to monitor progress and to step up care as and when required. There may also be a number of wellbeing resources available across localities.

Beating the Blues	cCBT programme for mild to moderate symptoms of depression and/or anxiety: 8 sessions	Link
Living Life	Appointment based telephone support for anxiety and depression for ≥16 years: 4-9 sessions	Link Tel: 0800 328 9655
Silvercloud	Range of online psychoeducational programmes to support wellbeing, stress and mild to moderate anxiety and low mood	Link
Sleepio	Online resource for Insomnia	Link
Daylight	Online resource for Anxiety	Link

[h] Silvercloud see 'How to assess for patient suitability for online mental health and wellbeing programs' for more detail

Appendix 3. Practice invitation letter for review

PRACTICE LETTERHEAD

Private & Confidential

Patient Name
Patient Address

Date

Dear

From reviewing your records, we note that you are currently prescribed *[drug name(s)]*.

With all medicines it is important that your *[drug name(s)]* is routinely reviewed in line with current guidelines and safety advice.

We are now inviting you to contact the practice to arrange a routine appointment where we can discuss your current use of *[drug name(s)]* and answer any questions and/or concerns you may have about your medications.

Yours sincerely

Drs A, B and C

Appendix 4. Patient information leaflet

Background
When used with non-drug treatments, antidepressants can be effective for the treatment of moderate to severe depression, moderate to severe anxiety disorders and nerve pain caused by diabetes and other conditions. However, there are concerns that some individual's may experience dependence and withdrawal associated with antidepressant use. It is also known that some individual's may receive appropriate course of treatment, while others may continue antidepressants inappropriately due to a lack of routine review.

What is the purpose of the antidepressant quality prescribing advice?
It is intended to:

- Empower and help people who receive antidepressants and prescribers to review antidepressants, and get the best out of the medicines for individual's.
- Improve the support available from the healthcare system for people experiencing dependence on, or withdrawal from, prescribed medicines.
- Help prescribers identify people who may benefit from an antidepressant review, and support routine antidepressant reviews.
- Provide a range of options, where appropriate, for people have completed their course of antidepressant treatment, and/or are appropriate to reduce and stop their antidepressants.

Do I need to have my antidepressant reviewed?

- Antidepressants are no different to any other medicines. It is important to have your medicines routinely reviewed. For some individual's once a year review may be enough, for others more regular review will be needed.
- Having medicines reviewed regularly creates an opportunity to discuss if a medicine needs to continue, and consider effective non-drug treatments and lifestyle changes that may help.

Do I need to stop my antidepressant?

- It may be appropriate for some individual's to stop their antidepressant, but not for others.
- Continuing your antidepressant maybe appropriate because there are more benefits to continuing than risks of stopping e.g. recurrence of severe depression.
- Reducing and/or stopping your antidepressant may be necessary to reduce the risk of avoidable adverse drug effects and harms e.g. falls, confusion, sedation, etc. Or where you have completed your course of antidepressant treatment and recovered e.g. 6 months of antidepressant treatment due a single episode of depression.

How should I stop my antidepressant?
If you are ready to stop your antidepressant

- Arrange a review with your general practice doctor, pharmacist or nurse.
- Discuss stopping your antidepressant and agree if this is appropriate.
- If appropriate to stop, then plan and agree the best way to do this for you considering the options outlined in the antidepressant quality prescribing advice.