Lancashire & South Cumbria Medicines Management Group

NHS Lancashire & South Cumbria NHS Foundation Trust

Guidelines for Primary Care: Review of Dosulepin

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Background

This guidance has been produced to support clinical reviews of patients prescribed Dosulepin for depression in primary care.

Production of this guidance is because of a recent incident where a patient sadly died of a Dosulepin overdose following a family bereavement. There was a history of cardiac disease. Further exploration uncovered the finding that there are over 1,000 patients currently receiving prescriptions for Dosulepin in primary care networks within Lancashire and South Cumbria. Nationally, Lancashire and South Cumbria are in the 88th centile for prescribing of Dosulepin.

Contact details for Lancashire and South Cumbria NHS Foundation Trust if needed are provided at the end of the document

Introduction

Prescribers are reminded of the following:

- Dosulepin has a very small margin of safety between the (maximum) therapeutic dose and potentially fatal doses.
- Overdose is associated with a relatively high rate of mortality due to fatal cardiac arrhythmias and respiratory arrest. Dosulepin is more likely to result in cardiac arrhythmias and convulsions when taken in overdose compared with other tricyclic antidepressants. Death from Dosulepin overdose can occur
- Dosulepin is more toxic in overdose than other tricyclic antidepressants. A toxic dose of Dosulepin is considered 3mg/kg in adults. All children who have ingested any amount of Dosulepin must be referred for assessment.
- NICE considers that evidence supporting its tolerability relative to other antidepressants is outweighed by the increased cardiac risk and toxicity in overdose.
- Dosulepin is included in the NHSE list of items which should not routinely be prescribed in primary care . The guidance document states that Dosulepin prescribing in primary care should be exceptional. Recommendations to primary care are included as follows:

    - Do not initiate.
    - Deprescribe in patients currently prescribed this medicine.
    - Prescribe only if no other item or intervention is clinically appropriate.
    - Prescribe only if no other item or intervention is available.
    - Prescribe only if the decision has been made after a multidisciplinary team discussion.

- Dosulepin has an unfavourable cardiac profile, even within BNF dose guidelines.
- Dosulepin should not be used as an anxiolytic, for neuropathic pain or for its sedative effects to aid sleep.
- Dosulepin should not be stopped abruptly unless serious side effects have occurred.
- Dosulepin is associated with a high anticholinergic burden.
- In accordance with guidance issued by the Commission on Human Medicines, a limited number of tablets should be prescribed to reduce the risk of overdose for all patients, especially those at risk of suicide. A maximum prescription equivalent to 2 weeks' supply of 75 mg per day should be considered in patients with increased risk factors for suicide at initiation of treatment, during any dose adjustment, and until improvement occurs

Dosulepin for off-label indications

- Off label indications may include, but are not limited to, anxiety, insomnia, migraine and neuropathic pain.
- If the person is currently open to specialist services for the management of this condition, seek specialist advice on stopping or switching Dosulepin.
- Consider discontinuation of Dosulepin where this is being prescribed in primary care for an off-label indication.
- Discuss alternative management strategies with the person. This may include non-pharmacological management strategies e.g. sleep hygiene, psychological interventions for anxiety, physical and psychological therapy for neuropathic pain
- Amitriptyline is not recommended as an alternative to dosulepin for insomnia or anxiety.
- See section below on how to stop Dosulepin safely.

Review process and principles

- Identify all patients with Dosulepin on repeat prescription.
- Identify if the person is currently under a specialist (e.g. community mental health team) and involve them in decisions to discontinue or switch treatment.
- Invite the person for a face-to-face consultation.
- Explain to the person reasons for the review and provide reassurances; this may be an anxiety inducing change.
- Clarify the indication for Dosulepin prescribing by gathering information from the person/family/carers and healthcare records.
- Document all discussions and decision related to Dosulepin in the clinical record.

Stopping or switching Dosulepin to an alternative antidepressant?

- If the person is currently open to mental health services, seek specialist advice on stopping or switching Dosulepin.
- Antidepressant treatment should be continued for at least 6 months after remission of an episode of depression, increased to at least two years for those at risk of relapse. Where there is high risk of relapse and a history of severe depression prophylaxis may continue for longer than two years
- Patients are at particular risk of relapse if:
    - they have had two or more episodes of depression in the recent past, during which they experienced significant functional impairment
    - they have other risk factors for relapse such as residual symptoms, multiple previous episodes, a history of severe prolonged episodes, or of inadequate response.
    - unhelpful coping strategies e.g. avoidance, rumination
    - other chronic physical or mental health problems
    - personal, social, and environmental factors that contributed to their depression that are still present (e.g. unemployment, stress, financial problems, social isolation, poverty)
- Continuation of antidepressant treatment after full or partial remission may reduce the risk of relapse.
- Discuss with the person whether to continue a pharmacological treatment for depression based on their clinical needs and preferences.
- Where a person is deemed to lack capacity, apply the Best Interest Principle as set out in the Mental Capacity Act 2005

- Consider suitability of non-pharmacological options for the management of anxiety and depression that is less severe.
- If a shared decision is made to continue antidepressant treatment, switch to an alternative with a better safety profile.

How to stop Dosulepin safely

- There may be concerns about stopping antidepressant medication (relapse or withdrawal symptoms) and most people will need support to stop successfully.
- Offer regular reviews (face to face or telephone) to check progress and monitor mental state.
- Dosulepin should not be stopped abruptly unless serious side effects have occurred.
- The speed and duration of the withdrawal should be agreed with the person on an individual basis.
- Reduce the dose gradually. Unless there are reasons for more rapid discontinuation (e.g. side-effect burden), then consider reducing over weeks, or months depending on duration of use (typically over weeks if previously taken for months; and over months if previously taken for years). Reduce at each stage by a maximum of 50% of the current dose and consider smaller percentage reductions as the total dose gets lower. Be guided by the advice 'as you go lower go slower', particularly if the patient is finding withdrawal difficult). Ensure that any withdrawal symptoms have resolved before making the next dose reduction. **See exemplar reduction regimen below.** Given patients are likely to have been on treatment for many years, a very gradual reduction regimen over months is proposed
- Discontinuation may take weeks or months to complete successfully.
- Advise the person to seek help as soon as possible if symptoms of depression return or residual symptoms worsen.
- Discuss with the person psychological therapy for relapse prevention.
- Refer to NHS Talking Therapies (previously IAPT) if appropriate.
- Patient information leaflets are linked in the resources section below. This includes a **patient information leaflet on antidepressant withdrawal**

Exemplar discontinuation regimen

Option 1.

Stage	Prescribed Dose	Reduction interval
Step 1	150mg	Reduce every 2-4 weeks. If discontinuation symptoms emerge increase back to the dose on the previous step and reduce more gradually by increasing frequency between dose reductions and/or reducing in small decrements using the 25mg/5ml liquid
Step 2	125mg	
Step 3	100mg	
Step 4	75mg	
Step 5	50mg	
Step 6	25mg	
Step 7	20mg (4ml x 25mg/5ml liquid)	
Step 8	15mg (3ml x 25mg/5ml liquid)	
Step 9	10mg (2ml x 25mg/5ml liquid)	
Step 10	5mg (1ml x 25mg/5ml liquid)	
Step 11	2.5mg (0.5ml x 25mg/5ml liquid)	
Step 12	STOP	

Managing withdrawal symptoms

- Advise the person that they may experience withdrawal symptoms (insomnia, headaches, nausea, anxiety, flu-like symptoms) but the risk is minimised with gradual dose reduction.
- Reassure the person that withdrawal symptoms are usually mild with gradual dose reductions and often self-resolve within 1-2 weeks.
- Explain to the person that experiencing withdrawal symptoms does not mean they are having a relapse of their depression. Withdrawal symptoms usually start soon after the medication is reduced whereas the return of depression or anxiety takes longer (typically weeks or months).
- If a person experiences mild withdrawal symptoms, initially monitor them and provide reassurance. Do not make another dose reduction until the symptoms have resolved.
- If withdrawal symptoms are more severe, consider increasing Dosulepin to the previous dose and then attempt dose reduction in a smaller decrement once symptoms have resolved.

Switching Dosulepin to an alternative antidepressant

- There is no direct antidepressant replacement for Dosulepin.
- The decision of which antidepressant to switch to must be a shared decision with the person.
- Discuss with the person: past treatment history (efficacy and tolerability of previous antidepressants), potential side effects and potential interactions with other medicines or physical health conditions.
- When switching from one antidepressant to another, abrupt withdrawal should be avoided unless there has been a serious adverse event or serious side effects.
- The method of switching depends on several factors:
  1) How long the person has been taking Dosulepin and the current dose.
  2) The new antidepressant being prescribed during the switch
  3) The urgency of the switch (if less urgent then a more cautious switching approach can be used).
  4) The person's physical condition (more caution advised in older adults or those with co-morbidities).
  5) The risk of serotonin syndrome (higher risk if the person is taking other medication with serotonergic activity)
  6) The person's ability to understand a switching regimen (risk of medication errors). Provide written and verbal instructions on the agreed switching plan.
- Do not switch to amitriptyline due to increased risk of fatality in overdose.
- Options for switching may include SSRIs (e.g. Sertraline, Citalopram, Escitalopram, Fluoxetine), SNRIs (e.g. Venlafaxine, Duloxetine), NaSSAs (e.g. Mirtazapine, useful if sedative effect is required) or another TCA (e.g. Lofepramine, this is the safest TCA option for depression).
- Cautious cross-tapering is the preferred method of switching from Dosulepin to SSRIs, SNRIs and Mirtazapine
- Cross-tapering of Dosulepin is inadvisable with paroxetine, fluvoxamine and clomipramine
- The initial Dosulepin reduction in these examples is 50% of the current dose; this reduction may need to be done in smaller steps depending on the person's response and any withdrawal symptoms.

Example switch from DOSULEPIN to SERTRALINE	**Medication**	**Current dose**	**Week 1**	**Week 2**	**Weeks 3**	**Week 4**
	Dosulepin	150mg	75mg	50mg	25mg	STOP
	Sertraline	0mg	0mg	25mg	50mg	50mg Titrate according to response and tolerability

Example switch from DOSULEPIN to CITALOPRAM	Medication	Current dose	Week 1	Week 2	Weeks 3	Week 4
	Dosulepin	150mg	75mg	50mg	25mg	STOP
	Citalopram	0mg	0mg	10mg	20mg	20mg Titrate according to response and tolerability. Maximum daily dose of 20mg in the elderly

Example switch from DOSULEPIN to MIRTAZAPINE	**Medication**	**Current dose**	**Week 1**	**Week 2**	**Weeks 3**	**Week 4**
	Dosulepin	150mg	75mg	50mg	25mg	STOP
	Mirtazapine	0mg	0mg	15mg	15mg	30mg Titrate according to response and tolerability.

Example switch from DOSULEPIN to VENLAFAXINE	**Medication**	**Current dose**	**Week 1**	**Week 2**	**Weeks 3**	**Week 4**
	Dosulepin	150mg	75mg	50mg	25mg	STOP
	Venlafaxine	0mg	0mg	37.5mg daily	75mg daily	75mg daily Titrate according to response and tolerability.

- Switching from Dosulepin to another TCA (e.g. Lofepramine) may be carried out via a cautious cross taper or direct switch if there is more urgency. An example of each type of switch is provided below. Cross-tapering of Dosulepin is inadvisable with Clomipramine

Cautious cross taper

Example switch from DOSULEPIN to LOFEPRAMINE	**Medication**	**Current dose**	**Week 1**	**Week 2**	**Weeks 3**	**Week 4**
	Dosulepin	150mg	75mg	50mg	25mg	STOP
	Lofepramine	0mg	0mg	35mg* (half a tablet)	70mg	140mg daily Titrate according to response and tolerability.

*Lofepramine 70mg tablets are scored.

Direct switch

Example switch from DOSULEPIN to LOFEPRAMINE	**Medication**	**Current dose**	**Week 1**	**Week 2**
	Dosulepin	150mg	75mg	STOP
	Lofepramine	0mg	0mg	140mg Titrate according to response and tolerability

The Dosulepin should first be gradually reduced to the usual starting dose (50-75mg daily). Once reduced to the usual starting dose, Dosulepin can be stopped and the new TCA started the next day with the usual starting dose as per the BNF

What shall I do if patients do not want to stop or switch treatment?

The General Medical Council advise the following where patients want medicines you don't think will benefit them:

Sometimes, patients will ask for treatment or care that you do not think is in their clinical interests. In these situations, you should explore the reasons for their request, their understanding of what it would involve and their expectations about the likely outcome. This discussion will help you take account of the factors that are significant to the patient and assess whether providing the treatment or care could serve the patient's needs.

If, after discussion, you still think the treatment or care would not serve the patient's needs, you should not provide it. You should explain your reasons to the patient and explore other options that might be available, including their right to seek a second opinion.

https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/good-practice-in-prescribing-and-managing-medicines-and-devices/deciding-if-it-is-safe-to-prescribe

Some patients will have been prescribed dosulepin long term and may be unaware that this antidepressant is no longer recommended as a routine treatment because of an increased risk of cardiac side effects and toxicity in overdose.

Accessing support from Lancashire and South Cumbria NHS Foundation Trust

For general advice about discontinuation or switching of antidepressants not contained within the guideline use **Advice and Guidance** to obtain information.

Where patients have a history of severe or treatment resistant depression and have had prior contact with mental health services for management of their depression or in the event of a deterioration in mental health meeting criteria for referral to specialist mental health service, referral should be via Initial Response Services (IRS) using the contact information below

IRS Bay locality	0800 013 0710
IRS Blackpool, Fylde and Wyre	0800 013 0709
IRS Central and West Lancashire	0800 013 0708
IRS Pennine	0800 013 0707

Useful Resources

NHS Talking Therapies for anxiety and depression in Lancashire and South Cumbria

Choice and Medication Handy Fact Sheet. Coming off antidepressants

Choice and Medication Patient Information Leaflet. Anxiety

Choice and Medication Patient Information Leaflet. Depression

Choice and Medication Patient Information Leaflet. Insomnia

Choice and Medication Handy Fact Sheet. Insomnia and Sleep Hygiene

Choice and Medication Handy Fact Sheet. Serotonin Syndrome

Patient information on psychotropic medicines, including easy read and translated leaflets (21 languages currently) are available at https://www.choiceandmedication.org/lancashirecaretrust/

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