Dosulepin

Area Prescribing Committee Position Statement

The prescribing of dosulepin is <u>not supported</u> by Barnsley Area Prescribing Committee (APC) for any indication. Dosulepin has a grey classification on the formulary.

In line with NHS England and/or local guidance:

- ***No new patients should be initiated on dosulepin.***
- ***All patients currently prescribed dosulepin should have their prescription reviewed and dosulepin should be deprescribed.***
- ***If in exceptional (rare) circumstances, there is a clinical need for dosulepin to be prescribed in primary care, this should be undertaken in a cooperation arrangement with a multi-disciplinary team and/or other healthcare professional in primary or secondary care.***

Dosulepin is included in the NHS England guidance ***'Items which should not routinely be prescribed in Primary Care'*** with no routine exceptions.[1]

The use of dosulepin is associated with increased cardiac risk and toxicity in overdose.[1,2]

In Barnsley, primary care expenditure on dosulepin between March 2021 and February 2022 was approximately £31K.

The Medicines Management Team can support primary care prescribers in reviewing patients and deprescribing dosulepin.

<u>Background and Rationale [1,3]</u>

Dosulepin, formerly known as dothiepin, is a tricyclic antidepressant**. NICE CG90: Depression in Adults** has a "do not do" recommendation: "*Do not switch to, or start, dosulepin because evidence supporting its tolerability relative to other antidepressants is outweighed by the increased cardiac risk and toxicity in overdose."*

Dosulepin is contraindicated in patients who have had a recent myocardial infarction or in patients with heart block of any degree or other cardiac arrhythmias. It is also contra-indicated in mania and in severe liver disease.[2]

<u>Deprescribing [2]</u>

Patients under the care of a specialist should be referred back to consider suitability of switching in partnership. Patients at risk of suicide should be reviewed as a matter of urgency.

The risks associated with dosulepin and alternative treatment options should be discussed with the patient:

<u>Antidepressant no longer required</u>

Consider the possibility that the patient no longer needs to take an antidepressant at all. Reduce the dose of dosulepin gradually over 3-4 weeks before stopping. Dosulepin should not be stopped suddenly unless serious side effects have occurred as patients may experience unpleasant discontinuation symptoms.

A suggested withdrawal regimen for dosulepin is:

Current dose	Week 1	Week 2	Week 3	Week 4
150mg/day	100mg/day	50mg/day	25mg/day	STOP

Some people, for example those patients who have been prescribed dosulepin for many years or where withdrawal symptoms occur, may require a more gradual tapering of the dose. Discontinuation symptoms may include anxiety, flu like symptoms and insomnia. The doses selected and the speed at which they are reduced will need to be individualised for each patient. In some patients it may be more appropriate to reduce the dose every 2-4 weeks.

Switching to an alternative antidepressant

Switch to a safer alternative antidepressant that has fewer side effects. Prescribing of antidepressants should be in line with the relevant NICE and local depression guidance.[3,4] A generic SSRI (citalopram, sertraline, fluoxetine and escitalopram are included on the Barnsley Formulary - see costs below) should be used first line unless contraindicated.[4] SSRIs are as equally effective as other antidepressants and have a favourable risk–benefit ratio.[3] Fluoxetine, fluvoxamine and paroxetine are associated with a higher propensity for drug interactions than other SSRIs.[3]

The choice of a potential alternative antidepressant should be discussed with the patient and should take into account their depressive symptoms, relative side effects, physical illness and interactions with any other prescribed medicines.

Switching dosulepin to a SSRI - suggested guidance on switching:

Gradually reduce the dose of dosulepin to 25-50mg/day as per the above withdrawal regimen, then add in the SSRI at the usual starting dose. Then slowly withdraw the remaining dosulepin over 5-7 days. The switch should be tailored to the individual and carried out cautiously.

If switching to citalopram, prescribers are reminded that the maximum dose for adults is now 40mg daily (20mg daily for over 65s) in view of the European-wide review into the risks of QT interval prolongation.[5] If switching to escitalopram, the maximum dose for adults is 20mg daily (10mg daily for over 65s).[5]

SSRIs are associated with an increased risk of bleeding, especially in older people or in people taking other drugs that have the potential to damage the gastrointestinal mucosa or interfere with clotting. In particular, consider prescribing a gastroprotective drug in older people who are also taking non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin.[3]

Ensure that all patients (or their carers) fully understand how to manage their gradual discontinuation or managed switch to an alternative antidepressant to reduce the risk of withdrawal symptoms such as anxiety, flu like symptoms and insomnia. **All patients should be regularly reviewed during the switching process. A further review is recommended after switching/stopping to ensure compliance and appropriate response to treatment (if switched) or continued complete remission of symptoms if stopped.**

Continuation of dosulepin

All patients should be reviewed and if in exceptional (rare) circumstances the GP decides to continue the prescribing of dosulepin, the reason for continuing should be documented in the patient's record. Dosulepin should only be continued in exceptional circumstances where the prescribing clinician in cooperation with another healthcare professional (in primary or secondary care) considers that no other medicine or intervention is clinically appropriate and available for the patient.

The GP may wish to contact SWYPFT via the 'advice and guidance' service regarding more complex patients.

Note that it is more cost effective to prescribe dosulepin 75mg tablets as Prothiaden® 75mg tablets (see costs below).

Unlicensed indications

Alternative non-antidepressant options may be suitable for patients taking dosulepin for other indications. Refer to the relevant guidelines and the information in Appendix 1 on unlicensed indications which has been provided by SWYPFT. Dosulepin is licensed for the treatment of depressive illness in adults. Unlicensed indications include anxiety, neuropathic pain and insomnia.

Patient information

A patient information leaflet explaining the changes to dosulepin prescribing is available:
https://www.prescqipp.info/media/1393/patient-information-changes-to-dosulepin-prescribing.pdf

SWYPFT choice and medication website:
https://www.choiceandmedication.org/swyp/

Costs

Price comparison between dosulepin and SSRIs on the Barnsley Formulary – Drug Tariff April 2022 and MIMS April 2022

Product	Cost per 28 tablets/capsules
Dosulepin 25mg capsules	£1.04
Prothiaden® 75mg tablets	£2.97
Dosulepin 75mg tablets	£10.41
Citalopram 10mg tablets	£0.74
Citalopram 20mg tablets	£0.83
Citalopram 40mg tablets	£0.97
Sertraline 50mg tablets	£1.04
Sertraline 100mg tablets	£1.16
Fluoxetine 10mg capsules	£35.00 For cost-effective prescribing it is recommended that for patients requiring a 10mg dose, half a 20mg dispersible tablets (£3.44 for 28 tablets) or the 20mg/5ml oral solution (£3.62 for 70ml) are prescribed. Note that Fluoxetine 20mg/5ml oral solution **sugar-free** is more expensive at £12.95 for 70ml. Patients prescribed two or more 10mg tablets/capsules daily should be considered for dose optimisation where appropriate, e.g. 2 x 10mg tablets/capsules could be optimised to 1 x 20mg tablet/capsule.
Fluoxetine 10mg tablets	£57.61 For cost-effective prescribing it is recommended that for patients requiring a 10mg dose, half a 20mg dispersible tablets (£3.44 for 28 tablets) or the 20mg/5ml oral solution (£3.62 for 70ml) are prescribed. Note that Fluoxetine 20mg/5ml oral solution **sugar-free** is more expensive at £12.95 for 70ml. Patients prescribed two or more 10mg tablets/capsules daily should be considered for dose optimisation where appropriate, e.g. 2 x 10mg tablets/capsules could be optimised to 1 x 20mg tablet/capsule.
Fluoxetine 20mg capsules	£0.79
Fluoxetine 20mg dispersible tablets sugar free	£3.44

Fluoxetine 30mg capsules	£1.68
Fluoxetine 40mg capsules	£1.68
Fluoxetine 60mg capsules	£2.24
Escitalopram 10mg tablets	£1.07
Escitalopram 20mg tablets	£1.29

References

1. NHS England guidance 'Items which should not routinely be prescribed in Primary Care: Guidance for CCGs'. Version 2, June 2019. Available at: https://www.england.nhs.uk/wp-content/uploads/2019/08/items-which-should-not-routinely-be-prescribed-in-primary-care-v2.1.pdf Accessed <27.04.22>
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3. NICE CG90. Depression in adults: recognition and management. October 2009. Available at: https://www.nice.org.uk/Guidance/CG90 Accessed <27.04.22>
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5. MHRA. Citalopram and escitalopram: QT interval prolongation. December 2014 Available at: https://www.gov.uk/drug-safety-update/citalopram-and-escitalopram-qt-interval-prolongation Accessed <27.04.22>

Appendix 1: SWYPFT Dosulepin advice and guidance for unlicensed indications (for primary care).

Historically Dosulepin has been prescribed at low doses, typically <100mg/day, for unlicensed indications including anxiety, neuropathic pain, migraine/cluster headaches prophylaxis and insomnia.

Dosulepin is a tricyclic antidepressant (TCA) with potent anticholinergic binding profile, even at low doses and will contribute significantly to the patient's anticholinergic burden.

Unlike SSRIs, TCAs including Dosulepin, demonstrate a dose dependent response for treatment of depression, with doses >100mg/day typically required.

Doses less than 100mg maybe effective for neuropathic pain and sedation, but patients will still be at risk of adverse effects and avoidable harm e.g. anticholinergic side effects, confusion, falls and QTc prolongation/cardiac toxicity etc.

Many patients are prescribed low doses of Dosulepin continuously long-term. For many, Dosulepin may no longer be indicated, or alternative safer medication will be appropriate.

Prescribers and patients may wish to initially consider a trial of discontinuing Dosulepin, to confirm ongoing indication for medication.

Abruptly stopping Dosulepin should be avoided as withdrawal symptoms, particularly anticholinergic rebound, may present even at low doses. Dosulepin should be gradually tapered down over weeks, or months, depending on the individual's preference and/or needs.

The optimum rate of tapering is unknown and will vary depending on individual's needs, preference, age, clinical condition, other comorbidities and length of treatment.

Establishing a therapeutics relation is essential to successfully discontinuing medication like Dosulepin. Many patients will have prescribed Dosulepin for a long time and will have strong feeling regarding their medication and maybe reluctant to change. Patients should be encouraged to discuss any concerns they may have, these should be explored and addressed by the prescriber.

A tapering plan should be agreed jointly between the prescriber and the patient on how to proceed. Some patients may need a plan spanning a month to successfully wean off Dosulepin.

A practical approach to tapering and discontinuing Dosulepin would be to reduce by 25mg every 1-6 weeks down to stop. For patients struggling with withdrawal symptoms, revert to the previously lowest tolerated dose and consider a longer interval between incremental dose reductions. 25mg ON is the lowest dose practically dose of Dosulepin possible. Some patients may wish to consider taking 25mg on alternate nights before stopping.

For patients who are struggling to stop or anxious, consider asking the patient to miss a dose one day a week of their choice, increasing every 1-4 weeks to miss 2 days in a week, then 3 days in a week etc. This strategy is slow but may help empower patients to take control and build confidence.

For patients who are unable to stop Dosulepin or where there is a clear on-going unlicensed indication that requires a TCA, consideration should be given to switch to Amitriptyline.

Amitriptyline and Dosulepin have a similar receptor binding profile, with amitriptyline been slightly more potent than Dosulepin.

Amitriptyline is a TCA recommended for indications such as neuropathic pain, migraine prophylaxis etc.

Dosulepin 25mg ON can be switched directly to Amitriptyline 25mg ON.

For higher doses of Dosulepin, an attempt should be made to taper down the dose initially to 25mg ON, before switching to amitriptyline. All patients should be reviewed within 1-2 weeks of switching, the dose may need to be adjusted according to the patient's response and tolerability.

For some patients it may be easier to taper and discontinue amitriptyline than it is for Dosulepin as it is available in a smaller dosage form of 10mg tablets and as a liquid.

Avoid substituting with an alternative hypnotic medication, as many have similar adverse effects and poor outcomes.