Dosulepin Guidance: Stopping or switching to alternative therapy

The NHS England and NHSCC led clinical working group developed guidelines regarding a list of 18 products which they considered to be ineffective, unnecessary, inappropriate or unsafe for prescription on the NHS. Dosulepin was identified as a Products of low clinical effectiveness, where there is a lack of robust evidence of clinical effectiveness or there are significant safety concerns.

The following points summarise the reasons that dosulepin is not recommended for prescribing nationally, and in Waltham Forest CCG

- Dosulepin has a small margin of safety between the (maximum) therapeutic dose and potentially fatal doses.
- The NICE guideline on depression in adults recommends that dosulepin should not be prescribed for adults with depression because evidence supporting its tolerability relative to other antidepressants is outweighed by the increased cardiac risk and toxicity in overdose.
- Existing patients should be reviewed to assess their ongoing need and suitability for dosulepin, in view of the associated safety concerns. Patients at risk of suicide should be reviewed as a matter of urgency.
- Dosulepin has also been used 'off label' in other indications such as fibromyalgia and neuropathic pain. However the evidence for use in in this way is weak, and is not recommended.
- The lethal dose of dosulepin is relatively low and can be potentiated by alcohol and other CNS depressants.
- Dosulepin overdose is associated with high mortality and can occur rapidly, even before hospital treatment can be received. Onset of toxicity occurs within 4-6 hours. Every year, up to 200 people in England and Wales fatally overdose with dosulepin. Of these about 20% are accidental. Doses of 750 mg in adults (ten 75mg tablets) have been associated with fatalities. The risk of overdose can also extend to others in the household of the person for whom the drug is prescribed.
- The risks associated with dosulepin are highest in patients who:
    - currently or have in the past been dependent on alcohol, or are known to binge drink
    - currently or have in the past been dependent on or used CNS depressants long term (e.g. analgesics, benzodiazepines)
    - have a history of attempted suicide or suicidal ideation
- Dosulepin has an established link with a number of adverse cardiovascular effects (cardiac arrhythmias, conduction disorders, hypotension, tachycardia/arrhythmia QTc prolongation, cardiac failure and circulatory collapse) especially in the elderly.
- It 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.
- Dosulepin is marked as 'less suitable for prescribing' in the British National Formulary (BNF) because relative incidence and severity of side effects is higher than other antidepressants, together with the risk of toxicity, and potential drug interactions

Dosulepin should be avoided in many conditions, for example, patients with:

- Diabetes
- Epilepsy
- Mania
- Narrow-angle glaucoma
- Hepatic or renal impairment
- Symptoms suggestive of prostatic hypertrophy
- Undergoing electroconvulsive therapy
- Urinary retention
- Parkinson's disease
- Alzheimer's Disease
- Cardiac Disease
- Thyroid disease

Recommendations

- As Dosulepin still poses a significant risk to patients, prescribers should actively review all patients being prescribed this medicine and renew efforts to identify an alternative and safer antidepressant.
- Please refer to the sections below on 'reducing and stopping dosulepin' and 'switching to another antidepressant' for advice about reducing and withdrawing dosulepin slowly, and where dosulepin has been prescribed in depression, the potential alternatives.
- As per NICE Clinical Guidance (CG90): 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 should not be stopped suddenly unless serious side effects have occurred, as patients may experience unpleasant discontinuation symptoms. Slowly tapering the dose over three to four weeks can help prevent this.[4-6]
- Discontinuation symptoms may include anxiety, flu-like symptoms and insomnia. Some people may require a more gradual tapering of the dose if withdrawal symptoms occur. The doses selected and the speed at which they are reduced will need to be individualised for each patient.[4-6]
- Prescribing of antidepressants should be in line with the relevant NICE guidance. First line SSRIs are generic citalopram and sertraline.
- If switching to citalopram, prescribers are reminded that the maximum dose for adults is now 40mg daily [20mg daily for over 65s and in patients with hepatic impairment]. All available data on QT prolongation with citalopram [and escitalopram] has been subject to a Europe-wide review[8]. Coadministration of citalopram [or escitalopram] with medicines that prolong the QT interval is therefore contraindicated. Caution is also advised in patients taking concomitant medications known to increase plasma levels of citalopram [or escitalopram], and may necessitate SSRI dose reduction.
- 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[1]. In particular, consider prescribing a gastroprotective drug in older people who are also taking nonsteroidal anti-inflammatory drugs (NSAIDs) or aspirin.

Reducing and stopping dosulepin

Dosulepin should not be stopped abruptly unless serious side effects have occurred. Slowly tapering the dose over 3 to 4 weeks can help prevent discontinuation symptoms, which may include anxiety, flu-like symptoms and insomnia. Some people may require a more gradual tapering of the dose if withdrawal symptoms occur. The doses selected and the speed at which they are reduced will need to be individualised for each patient.
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

Switching from dosulepin to another antidepressant

There should be very close monitoring of patients being switched from dosulepin to another antidepressant, as there are no published guidelines to determine exactly how the switch should take place. The switch will need to be tailored to each individual and carried out cautiously. The regimen will depend upon how severe the depression is and which drug is being switched to. Gradual cross tapering is usually recommended, but in some cases a washout period between drugs is required, e.g. if switching to monoamine oxidase inihibitors (MAOIs). If cross tapering, it is important to bear in mind certain SSRIs can double or triple tricyclic levels so great care is needed. Very general guidance on switching from dosulepin to another antidepressant is as follows:

Dosulepin to an SSRI	Gradually reduce the dosulepin dose to 25 to 50mg / day then add the SSRI at usual starting dose. Then slowly withdraw the remaining dosulepin over 5-7 days.
Dosulepin to mirtazapine	Gradually reduce dosulepin dose to 25 to 50mg/day then add mirtazapine 15mg/day. Cross taper cautiously, increasing mirtazapine dose based on therapeutic response. Slowly withdraw the remaining dosulepin.
Dosulepin to venlafaxine	Cross taper cautiously starting with venlafaxine 37.5mg daily

Consideration should be given to relative side effects, current diagnosis and potential drug interactions with concurrently prescribed medication.

Patients under the care of a specialist should be referred back to consider suitability of switching in partnership.

Alternative non-antidepressant options may be suitable for patients taking dosulepin for other indications

Contact details for advice and support

North East London Foundation Trust	Access, assessment and brief intervention team
Redbridge	0300 300 1570 (option 1)
Havering	0300 300 1570 (option 2)
Barking & Dagenham	0300 300 1570 (option 3)

References

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