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Dosulepin (Prothiaden®): Guidance on withdrawal

Indication: Dosulepin is a tricyclic antidepressant (TCA) indicated in the treatment of depressive illness, especially where sedation is required.[i]

Formulary status: Not on formulary (but some patients may have been initiated and maintained historically). Note: When an antidepressant is to be prescribed, TCAs are no longer considered first line treatment for depression due to their side effect profile. SSRIs are equally effective as other antidepressants and have a favourable risk-benefit ratio. [ii] Dosulepin is effective but known to be particularly dangerous in overdose and now not recommended for treatment of depression.

Dose: In the treatment of depression, the usual initial dose is 75 mg daily in divided doses *or* as a single dose at bedtime, increased if necessary to 150 daily. Doses can be increased gradually up to 225mg daily in some circumstances (e.g hospital use). The recommended initial dose for the elderly in the UK is 50-75 mg daily which should be increased with caution under close supervision.

Unlicensed uses: Neuropathic pain/chronic pain, insomnia, anxiety.

Mode of action: Serotonin and noradrenaline reuptake inhibitor.

- **Anticholinergic activity** may cause dry mouth, constipation and blurred vision.
- **H1 blockade** may cause sedation.
- **Adrenergic alpha 1 receptor blockade** may cause dizziness, sedation and hypotension.
- **Ion channel blockade** may cause cardiac arrhythmias and seizures especially in overdose.[iii]

Reasons for caution: Reports of cardiac arrhythmias, QTc prolongation, sinus tachycardia, orthostatic hypotension. Drug interactions. High rate of fatality in overdose.

Side effects:

- As listed above

Guidance and recommendations:

- No new patients should be prescribed dosulepin.
- Patients currently prescribed dosulepin should be identified and have their treatment history reviewed. Where possible dosulepin should be gradually withdrawn and stopped if no longer clinically indicated.
- Suitable alternatives may include an SSRI such as sertraline, mirtazapine (if a sedative antidepressant is required), imipramine or lofepramine if an alternative TCA is required. Individual product literature for each of these medicines is available from www.medicines.org.uk
- TCAs should not be terminated abruptly (unless a serious adverse event has occurred e.g. cardiac arrhythmia), instead gradually taper down the daily dose in weekly/two weekly decrements[iv] over **at least** 4 **weeks** to avoid withdrawal effects. [v]
- For patients who have been taking dosulepin for long term maintenance treatment (>1 year), more gradual tapering may be appropriate, in the region of at least 6 months.[v]
- Even with a gradual dose reduction some withdrawal symptoms may appear within the first 5 days.[v] As with all swaps in medication tailor the withdrawal process to the individual patient, monitoring patient tolerability.

- In patients taking a split daily dose, the morning dose should ideally be completely reduced first before withdrawing the night time dose to minimise the change in effects on night-time sedation.

Few studies have specifically examined the best strategy for switching between antidepressants. The following advice is based on available information, theoretical concerns and clinical experience. It is intended for general guidance only.[iii]

Suggested withdrawal and crossover to mirtazapine schedule
(e.g. where sedative action required)

Drug	Current dose	Week 1	Week 3	Week 5	Week 7
Dosulepin	75mg/day	50mg/day	25mg/day	25mg/ alternate days	STOP
Mirtazapine	Nil	Nil	15mg/day (at night)	30mg/day (at night)	Further dose ↑ based on response

Suggested withdrawal and crossover to imipramine/lofepramine schedule[iv v]
(e.g. where anxiolytic action required)

Drug	Current dose	Week 1	Week 3	Week 5	Week 7
Dosulepin	75mg/day	50mg/day	25mg/day	20mg/alternate days	STOP
Imipramine* *Recommended [vi] elderly doses	Nil	Nil	10mg/day (at night)	20mg/day (at night)	Further dose ↑ based on response.
Lofepramine	Nil	Nil	70mg twice daily	70mg twice daily	Further dose ↑ based on response.

Practical considerations:

- Issue 7 day scripts for safety reasons and to reduce waste
- Dosulepin is available as 25mg and 75mg tablets and capsules. Limit the prescribing for safety reasons and to make regimes simpler whilst reducing doses.
- Tailor the withdrawal and cross over process to the individual patient based on efficacy and tolerability.
- If the patient experiences any withdrawal effects then return to the previous dose of dosulepin and continue with the cross over at a slower pace using smaller decrements.
- Information on good sleep hygiene and non-pharmacological techniques may be found at www.nhs.uk/conditions/insomnia. Consider short term use of zopiclone but note risk of tolerance, addiction and falls risk.

Suggested monitoring:
BP, pulse, weight, BMI, U&E, eGFR, LFTS, full annual health check. (ECG as required)

References:

[i] Dosulepin SPC. MHRA.gov.uk [Accessed 26/11/2017]
[i] CG90. Published date: October 2009. Last updated: April 2016. https://www.nice.org.uk/guidance/cg90
[iii] Maudsley Prescribing Guidelines Antidepressants. 12th Edition.
[iv] https://www.sps.nhs.uk/articles/how-do-you-switch-between-tricyclic-ssri-and-related-antidepressants/ [Accessed: 26/11/2017]
[v] Joint Formulary Committee. British National Formulary [Online] London: BMJ Group and Pharmaceutical Press Available: http://www.medicinescomplete.com [Accessed: 26/11/2017]