Trimipramine – stopping & switching guidance

Summary

- Trimipramine is a tricyclic antidepressant which is no longer recommended by NICE, NHSE, Hertfordshire Partnership Foundation Trust (HPFT), Essex Partnership University Trust (EPUT) or Herts and West Essex Integrated Care Board
- Patients should NOT be initiated on or switched to trimipramine.
- For existing patients, it may be appropriate to stop trimipramine or switch to another antidepressant.
- In **exceptional** cases there may be a clinical need to continue trimipramine. In these cases, the decision should be made in conjunction with a consultant or other specialist healthcare professional.

Background and rationale

- The tricyclic antidepressant (TCA) trimipramine is significantly more expensive than other antidepressants.
- NICE guidance on depression in adults recommends selective serotonin reuptake inhibitor (SSRI) antidepressants first line if are indicated as they have a more favourable risk-to-benefit ratio compared to TCAs. However, if a TCA is required, more cost-effective TCAs than trimipramine are available.
- TCAs and monoamine oxidase inhibitors (MAOIs) have the highest toxicity in overdose compared to other antidepressants.

Recommended actions

- Do not initiate or switch to trimipramine in any patients.
- Existing patients should be reviewed in line with current NICE clinical guidance to assess their ongoing need and suitability for trimipramine. Consideration should be given as to whether trimipramine should be switched to an alternative or treatment stopped entirely.
- Trimipramine should not be prescribed for any unlicensed indication, including anxiety, neuropathic pain, fibromyalgia or insomnia.
- Patients under the current or recent care of a specialist should be referred back to the specialist.
- Document the outcome of discussions and clearly identify the reason(s) if continuing trimipramine.

Suggested review process

- Practice pharmacists should prioritise reviewing these patients.
- This guidance document focusses on deprescribing or switching trimipramine when it has been initiated as an anti-depressant. There are many alternative, safe, cost effective antidepressants available and review of trimipramine for this indication should be considered a practice priority.
- Patients who are on dual antidepressant therapy with trimipramine should be referred to a secondary care specialist for advice and support to deprescribe/switch
- Patients who are taking trimipramine for an indication other than depression may need to be referred back to their initial prescribing team for advice and support to deprescribe.
- Trimipramine is **non-formulary** across HWE ICB.

Stopping or switching

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. 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, or a history of severe prolonged episodes, or of inadequate response.

Prior to discontinuation there should be a full discussion of the potential consequences of relapse, taking into account previous history (including suicide attempts, loss of functioning, severe life disruption, inability to work or manage childcare). The timing of discontinuation should include a consideration of social context.

Where a decision is taken to switch from trimipramine to another antidepressant medication, be aware that there is no direct replacement for trimipramine. The decision of which alternative to use should be discussed with each individual patient. Considerations will include relative side effects, current diagnoses, past treatment history (including tolerability and effect of previous antidepressant medications) and potential drug interactions with other prescribed medication.

Reducing and stopping trimipramine

Any discontinuation of therapy should be carried out slowly, with gradual dose reductions, for patients who have been taking an antidepressant regularly for six weeks or more. Withdrawal effects may occur within five days of stopping treatment with antidepressant drugs. These are usually mild and self-limiting but, in some cases, can be severe. Common symptoms include flu-like symptoms (chills, myalgia, excessive sweating, headache, and nausea), insomnia and excessive dreaming. Occasionally movement disorders, mania and cardiac arrhythmias may be seen.

Treatment of discontinuation symptoms is pragmatic. If symptoms are mild, it may be enough to simply reassure the patient that such symptoms are not uncommon and that they normally pass in a few days. If symptoms are more severe, the original antidepressant should be re-introduced (or another from the same class but with a longer half-life), and then tapered off much more gradually while closely monitoring for further symptoms.

Reduce dose gradually over at least 4 weeks or longer if withdrawal symptoms emerge. **For patients who have taken trimipramine for several years, consideration should be given to a more graduated/slower withdrawal.**

Switching from trimipramine to another antidepressant

There should be very close monitoring of patients being switched from trimipramine 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, particularly in the elderly. The regimen will depend upon how severe the depression is, the dose of trimipramine prescribed, length of time it has been prescribed and which drug is being switched to. Please refer to the individual SmPCs for further guidance regarding dosing in the elderly, as this may differ to that recommended for younger adults. Gradual cross tapering is usually recommended but in some cases a washout period between drugs is required.

When switching to SSRIs or venlafaxine there is a risk of **serotonin syndrome** especially in those taking other serotonergic medications.

Whilst moving to another antidepressant option, it would be prudent to ONLY provide small supplies of trimipramine and/or the new drug and to review the patient often.

The following tables are interpretations of the advice given in The Maudsley Prescribing Guidelines and the BNF and provide some additional guidance on how to manage switching, however, the speed of cross-tapering is best judged by individual patient tolerability and response. If patients are not tolerating the change, cross-taper more slowly. The lowest effective dose of the replacement antidepressant should be used and adjusted individually according to the patient's response. Please note, doses below are represented as *total daily doses* and do not reflect frequency.

Switching from trimipramine to an SSRI

Start by halving the dose of trimipramine then add the SSRI and cross-taper over four weeks, or as deemed appropriate taking into consideration individual patient factors.

	Medication	Current total daily dose	Week one	Week two	Week three	Week four
Switching from trimipramine 150mg daily dose to an SSRI (minimum effective dose)	Trimipramine	150mg daily	75mg daily	50mg daily	25mg daily	Stop
	Sertraline	-	25mg daily	50mg daily	50mg daily	If necessary, start to titrate sertraline up by 50mg at intervals of at least one week until minimum effective dose reached. Maximum daily dose 200mg.
	OR					
	Citalopram	-	10mg daily	20mg daily	20mg daily	If necessary, start to titrate up by 10mg at intervals of at least 2 weeks until minimum effective dose reached. Maximum daily dose 40mg (20mg in elderly).

For patients who have taken trimipramine for several years, a more cautious cross-taper may be considered.
Doses are represented as *total daily doses* and do not reflect frequency.
See the SmPC for citalopram drops section 4.2 for dose equivalence between tablets and liquid.

Switching from trimipramine to an alternative TCA

Cross tapering between two different tricyclic antidepressants should be done cautiously, taking into consideration individual patient risk factors.

	Medication	Current total daily dose	Week one	Week two	Week three	Week four	Week five
Switching from	Trimipramine	150mg daily	100mg daily	75mg daily	50mg daily	25mg daily	Stop

trimipramine 150mg daily dose to alternative TCA (minimum effective dose)	Imipramine	-	25mg daily	50mg daily	75mg daily	100mg daily	If needed dose can be taken to 150mg-200mg daily. Maintain this dose until improvement is seen then gradually reduce to a maintenance dose of 50mg to 100mg daily, (the elderly may respond to lower doses – refer to SmPC).
	OR						
	Lofepramine	-	-	70mg daily	70mg daily	140mg daily	Usual total daily dose 140mg (the elderly may respond to lower doses – refer to SmPC). Maximum total daily dose 210mg.

For patients who have taken trimipramine for several years, a more cautious cross-taper may be considered. Doses are represented as *total daily doses* and do not reflect frequency.

Switching from trimipramine to mirtazapine

TCAs should be cross tapered cautiously to mirtazapine, taking into consideration individual patient risk factors.

	Medication	**Current total daily dose**	**Week one**	**Week two**	**Week three**	**Week four**	**Week five**
Switching from trimipramine 150mg daily dose to mirtazapine (minimum effective dose)	Trimipramine	150mg daily	100mg daily	75mg daily	50mg daily	25mg daily	Stop
	Mirtazapine	-	-	15mg daily	15mg daily	30mg daily	If necessary, start to titrate up by 15mg at intervals of at least one week until minimum effective dose reached. Maximum daily dose 45mg.

For patients who have taken trimipramine for several years, a more cautious cross-taper may be considered. Doses are represented as *total daily doses* and do not reflect frequency.

Switching from trimipramine to venlafaxine (SNRI)

Tricyclics should be cross tapered to venlafaxine cautiously, taking into consideration individual patient risk factors.

Venlafaxine is available in both standard release (usually twice daily dosing) and XL (usually once daily) preparations. A lower dose of 37.5mg is available in both standard & XL preparations if required.

The dose can be increased gradually by 37.5 -75mg mg at intervals of at least two weeks until the minimum effective dose is reached. *Doses over 300mg/day should only be prescribed under the supervision or advice of a specialist mental health practitioner.

	Medication	Current total daily dose	Week one	Week two	Week three	Week four	Week five
Switching from trimipramine 150mg daily dose to venlafaxine (minimum effective dose)	Trimipramine	150mg daily	100mg daily	75mg daily	50mg daily	25mg	Stop
	Venlafaxine	-	-	37.5mg daily	37.5mg daily	75mg daily	If necessary, dose can be titrated up at intervals of at least two weeks until minimum effective dose reached. Maximum daily dose 375mg*.

For patients who have taken trimipramine for several years, a more cautious cross-taper may be considered. Doses are represented as *total daily doses* and do not reflect frequency.

Resources

- A local patient information leaflet to support the changes is available at: https://www.hweclinicalguidance.nhs.uk/all-clinical-areas-documents/search-results/trimipramine-info/
- Drug Titration and Review for Neuropathic Pain Pathway
- An example patient review template for practice use is embedded below. This can be adapted for local use and may be helpful when undertaking the individual reviews.

Patient review template de-prescribi

References:

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Version:	1.0
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Ratified by	Medicines Optimisation and Delivery Group (MODIG), May 2024
Review date	May 2027