Trimipramine

Barnsley Area Prescribing Committee Position Statement

The routine prescribing of trimipramine is <u>not supported</u> by Barnsley Area Prescribing Committee (APC). Trimipramine has a grey non formulary classification.

In line with NHS England guidance 'Items which should not routinely be prescribed in Primary Care' :[1]

- ***No new patients should be initiated on trimipramine.***
- ***Patients currently prescribed trimipramine should have their prescription reviewed and trimipramine should be deprescribed.***
- ***Trimipramine should be prescribed only if no other item or intervention is clinically appropriate or available.***

Trimipramine is a tricyclic antidepressant (TCA) which is no longer recommended by NICE, NHS England or Barnsley APC as the price of trimipramine is significantly more expensive than other antidepressants (See Appendix 1).[1,2]

In Barnsley, primary care expenditure on trimipramine tablets between September 2022 and August 2023 was approximately £18.7K.

The Medicines Management Team can support primary care prescribers in reviewing patients and deprescribing trimipramine tablets. Further information on deprescribing and switching to alternative antidepressants can also be found in the PrescQIPP bulletin available at: https://www.prescqipp.info/umbraco/surface/authorisedmediasurface/index?url=%2fmedia%2f6258%2f311-trimipramine-20.pdf

Background and rationale

- Trimipramine has been included in the NHS England guidance 'Items which should not be routinely prescribed in primary care' as even though it is clinically effective, more cost-effective products are available.[1]
- NICE guidance (NG222) Depression in adults: treatment and management, recommends primary care prescribers should offer serotonin reuptake inhibitors (SSRIs) as the first-line antidepressant medication treatment option for depression, as they are equally effective and have a more favourable risk-benefit ratio compared to TCAs.[1,2,3] However, if a TCA is required, more cost-effective TCAs than trimipramine are available.[1,2] Trimipramine is a tricyclic antidepressant with sedative properties. Tricyclic antidepressants also have varying degrees of antimuscarinic and cardiotoxicity in overdosage.[2] Lofepramine has the best safety profile.[3]

Deprescribing[2]

Antidepressant treatment should be continued for at least six months (and for some time after symptoms remit).[3] Ongoing prescribing of antidepressants to prevent relapse should be reviewed at least every six months. [2] A face to face review should be arranged for all patients aged 18 and over currently prescribed trimipramine to ensure that prescribing is in line with local and national guidance and cost-effective. Liaise with the specialist if the patient is currently under their care. Patients under 18 should be referred to the specialist to review. Discuss **alternative treatment options** for depression with the patient using the following options as a guide, this should be tailored to the individual patient. Patients at risk of suicide should be reviewed as a matter of urgency.[2]

If trimipramine is being prescribed for an **unlicensed indication** (e.g. anxiety, neuropathic pain, fibromyalgia or insomnia) consider discontinuation or switching treatment to a more appropriate alternative. Liaise with the appropriate specialist where necessary.[2]

Reducing and stopping trimipramine

A trial discontinuation of trimipramine should be considered if long term maintenance is no longer considered to be needed. Advise patients that it is usually necessary to reduce the dose in stages over time (called 'tapering') and they may experience withdrawal symptoms (Appendix 3) during tapering. Withdrawal symptoms do not affect everyone and can vary in type and severity between individuals. Trimipramine should not be stopped abruptly unless serious side effects have occurred. [2]

When stopping a person's antidepressant medication take into account:[2]

- The pharmacokinetic profile (for example, the half-life of the medication as antidepressants with a short half-life will need to be tapered more slowly) and the duration of treatment.
- Slowly reduce the dose to zero in a step-wise fashion, at each step prescribing a proportion of the previous dose (for example, 50% of previous dose).
- Consider using smaller reductions (for example, 25%) as the dose becomes lower.
- If, once very small doses have been reached, slow tapering cannot be achieved using tablets or capsules, consider using liquid preparations if available.
- Ensure the speed and duration of withdrawal is led by and agreed with the person taking the prescribed medication, ensuring that any withdrawal symptoms have resolved or are tolerable before making the next dose reduction.
- Take into account the broader clinical context such as the potential benefit of more rapid withdrawal if there are serious or intolerable side effects (for example, hyponatraemia or upper gastrointestinal tract bleeding).
- Take into account that more rapid withdrawal may be appropriate when switching antidepressants.
- Recognise that withdrawal may take weeks or months to complete successfully.

Further information on stopping treatment can be found in Appendix 2.

When reducing the dose of trimipramine, it should be done gradually over at least four weeks, or longer if withdrawal symptoms emerge (six months in patients who have been on long term maintenance treatment).[2] Further information on withdrawal effects can be found in Appendix 3.

Switching from trimipramine to another antidepressant

Where antidepressant treatment is still indicated, NICE recommends using SSRIs in a generic form as the first-line treatment option due to their more favourable risk/benefit ratio and better tolerated by patients. However, 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.[2] In particular, consider prescribing a gastroprotective drug in older people who are also taking non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin[7].

If an SSRI isn't appropriate and an alternative tricyclic antidepressant would be a more suitable alternative, there are more cost-effective TCAs than trimipramine available[2]. A trial of lofepramine should be considered as it has the best safety profile.[3]

- When switching from one antidepressant to another, be aware of the need for gradual and modest increases of dose, interactions between antidepressants, and the risk of serotonin syndrome when combinations of serotonergic antidepressants are prescribed.
- Abrupt withdrawal should generally be avoided when switching from one antidepressant to another.
- Cross tapering is usually preferred. However, cross-tapering with a tricyclic antidepressant is inadvisable with paroxetine and fluvoxamine, if necessary it should be done very cautiously.
- Clomipramine is a potent inhibitor of serotonin reuptake and serotonin syndrome is more likely if co-administered with an SSRI or SNRI, cross-tapering is not recommended except under specialist supervision.

Further information on switching from a tricyclic antidepressant can be found in Appendix 4 and from the NICE CKS on Switching antidepressants: Switching antidepressants | Prescribing information | Depression | CKS | NICE

Further help and advice

- A **patient information leaflet** explaining the changes to trimipramine prescribing is available at: https://www.prescqipp.info/media/1407/patient-information-changes-to-trimipramine-prescribing.pdf

- The patient can also be directed to the SWYPFT choice and medication website which has lots of patient information for medicines used in Mental Health: https://www.choiceandmedication.org/swyp/

References

1. NHS England guidance 'Items which should not routinely be prescribed in Primary Care: Guidance for CCGs'. August 2023. Available at: NHS England » Items which should not routinely be prescribed in primary care: policy guidance Accessed <14.11.23>
2. PrescQIPP CIC Drugs to Review for Optimised Prescribing – Trimipramine 2.0 August 2022. Available at: https://www.prescqipp.info/umbraco/surface/authorisedmediasurface/index?url=%2fmedia%2f6258%2f311-trimipramine-20.pdf Accessed <14.11.23>
3. NICE Depression in adults: treatment and management (NG222). Published June 2022. http://www.nice.org.uk/guidance/ng222 Accessed <14.11.23>
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7. Clinical Knowledge Summary. Depression. Last revised July 2023. http://cks.nice.org.uk/topics/depression/ Accessed <11.14.23>

Appendix 1 - Costs

Trimipramine price comparison with other antidepressants (Drug Tariff November 23).[6]

Drug	Class of antidepressant	Usual maintenance dose	Cost per 28 tablets or capsules (£)
Trimipramine 10mg tablets	TCA	75-150mg daily	£179.18
Trimipramine 25mg tablets	TCA	75-150mg daily	£200.50
Trimipramine 50mg capsules	TCA	75-150mg daily	£217.50
Imipramine 10mg tablets	TCA	50-200mg daily	£1.40
Imipramine 25mg tablets	TCA	50-200mg daily	£1.32
Citalopram 10mg tablets	SSRI	20-40mg daily (adults) 10-20mg daily (elderly)	£0.85
Citalopram 20mg tablets	SSRI	20-40mg daily (adults) 10-20mg daily (elderly)	£1.03
Citalopram 40mg tablets	SSRI	20-40mg daily (adults) 10-20mg daily (elderly)	£0.96
Fluoxetine 10mg capsules	SSRI	20-60mg daily	£15.16
Fluoxetine 20mg capsules	SSRI	20-60mg daily	£0.94
Fluoxetine 30mg capsules	SSRI	20-60mg daily	£2.97
Fluoxetine 40mg capsules	SSRI	20-60mg daily	£2.33
Fluoxetine 60mg capsules	SSRI	20-60mg daily	£2.00
Sertraline 50mg tablets	SSRI	50-200mg daily	£0.96
Sertraline 100mg tablets	SSRI	50-200mg daily	£1.11

Appendix 2 - Suggested guidance on stopping trimipramine

Please note, doses below are represented as total daily doses and do not reflect frequency.

Reduce dose gradually over at least four weeks or longer if withdrawal symptoms emerge.

Current daily dose	Current daily dose	Week one	Week two	Week three	Week four
Reducing from trimipramine 150mg daily dose	150mg daily	100mg daily	50mg daily	25mg daily	Stop
Reducing from trimipramine 100mg daily dose	100mg daily	75mg daily	50mg daily	25mg daily	Stop
Reducing from trimipramine 75mg daily dose	75mg daily	50mg daily	25mg daily	10mg daily	Stop

Appendix 3 - Withdrawal effects

Due to the risk of discontinuation syndrome with sudden cessation of therapy with antidepressants, discontinuation and switching must be managed carefully. Dosage adjustments should be made carefully on an individual patient basis, to maintain the patient at the lowest effective dose. Dosage during long term therapy should be kept at the lowest effective level, with subsequent adjustment depending on therapeutic response. Any discontinuation of therapy should be done slowly, with gradual dose reductions, for patients who have been taking an antidepressant regularly for six weeks or more. When changing from one antidepressant to another, abrupt withdrawal should usually be avoided. Any switching should be carried out with the appropriate gradual cross-tapering regimen. Patients should be very carefully monitored and reviewed to reduce the risk of withdrawal effects.

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.

Withdrawal effects may occur within five days of stopping treatment with antidepressant drugs. They are usually mild and self-limiting but in some cases can be severe. The risk of withdrawal symptoms is increased if an antidepressant is stopped suddenly after regular administration for eight weeks or more.

Common symptoms:

- Flu-like symptoms (chills, myalgia, excessive sweating, headache, nausea)
- Insomnia
- Excessive dreaming.

Occasionally:

- Movement disorders
- Mania
- Cardiac arrhythmias.

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.

Appendix 4- Switching from a tricyclic antidepressant (except clomipramine)[2]

Switching to	
TCA (except clomipramine)	Direct switch possible
SSRI (citalopram, escitalopram, paroxetine or sertraline)	Gradually reduce the dose of tricyclic to 25–50mg daily or half the usual dose Start SSRI then slowly withdraw tricyclic over next five to seven days
SNRI (duloxetine, venlafaxine)	Cross-taper cautiously starting with low dose SNRI
Fluoxetine	Halve dose of tricyclic Add fluoxetine and then slowly withdraw tricyclic
Mirtazapine	Cross-taper cautiously
Moclobemide	Taper then stop tricyclic, then wait for one week then start moclobemide
Reboxetine	Cross-taper cautiously
Trazodone	Halve dose of tricyclic, add trazodone and then slowly withdraw tricyclic