

Standard Operating Procedure (SOP) to review the of prescribing of Trimipramine

This is a CCG SOP that would be used by the CCG staff to complete this piece of work. If you want to utilise this, please adapt it to meet your own needs in practice.

Context

Trimipramine is a tricyclic antidepressant (TCA). It is licensed for the treatment of depressive illness particularly where sedation is required. Onset of sedation is achieved within 24hrs and the antidepressant action follows within 7-10days. The strength of Trimipramine comes as 10mg, 25mg and 50mg. The regular dose of Trimipramine in Adults: initiated at 50-75mg/day and stabilised at a maintenance dose of 75-150mg/day.

As is the case with other tricyclic antidepressants, Trimipramine may cause fatality in over dosage and should not be used first line for the treatment of depression. Trimipramine has also been subject to excessive price inflation. Amitriptyline, which is a comparable drug to Trimipramine, at a dose of 50mg to 150mg daily costs £1.55 to £4.65 per month whereas Trimipramine 50mg to 150mg daily costs £217.50 to £652.50 per month (Drug Tariff online August 2021 prices).¹

Selective Serotonin Reuptake Inhibitors (SSRI's) are recommended by NICE as they are equally effective, less toxic and have a more favourable cost to benefit ratio². The dosing schedule of SSRI's being mostly once daily supports compliance as Trimipramine requires more dosage titration reducing patient adherence. Trimipramine is not recommended at all for children and adolescents under the age of 18 years as the risks significantly outweigh the benefits (see PrescQIPP Bulletin B204 and NHSE guidance August 2019)^{3,4}

When using this SOP ensure you are up to date with and access relevant guidelines and reference sources including the BNF, drug alerts, individual drug summary of product characteristics, NICE guidelines and information from NICE Clinical Knowledge Summaries (CKS).

Audit aims

The aim of the audit is to review all prescribing of Trimipramine, with a view to implementing one of the options detailed in the audit objectives.

Audit Objectives

100% of Trimipramine prescribing should be reviewed which results in one of the following outcomes, as deemed appropriate for the individual patient:

1. To gradually de-prescribe.
2. To switch to an alternative antidepressant that is appropriate for the individual patient via a cautious cross-tapering approach.
3. To seek specialist support – if patient is very concerned about stopping or changing treatment.

Review process

1. All healthcare professionals must ensure they act within their sphere of competence and are up to date with this clinical area before implementation of this SOP.
2. The principal aim of the review is to either de-prescribe Trimipramine or change treatment to a more suitable alternative.
3. The GP Prescribing Lead or Designated Clinician (DC)* acting in accordance with this SOP should tailor the review according to the circumstances of the patient. Only general information is provided here.
4. For patients who are taking Trimipramine regularly the GP/DC may have to support the patient throughout the process during which the drug is being de-prescribed or the treatment is being changed to a more suitable alternative.
5. The GP/DC will have to ensure that appropriate arrangements are in place at the practice for any prescribing, issuing of prescriptions and notifying of patients that are required as part of the treatment change.
6. At the outset, agree with the GP Prescribing Lead at the practice the plan to review the treatment. The practices' GP Prescribing Lead must be provided with a copy of this SOP. Agree this SOP with the practices' GP Prescribing Lead and document the following:

Designated Clinician who will be working to this SOP	
Job title of Designated Clinician who will be working to this SOP	
Name of GP Prescribing Lead	
Signature of GP Prescribing Lead/DC authorising work in accordance with this SOP (prior to authorisation, the <u>(prior to authorisation, the GP/DC must ensure that this is within the scope of practice of the Pharmacist/Pharmacy professional who will be working to this SOP)</u>)	
Date of authorisation	
Time frame for completion of work in accordance with this SOP	
Communication method to discuss changes with the patient and to agree the plan (e.g. face-to-face reviews and for follow up reviews telephone calls at the very least)	

7. Once approval to work in accordance with this SOP has been received, inform practice staff (e.g. via a practice meeting or an email) of the plan to carry out this piece of work.
8. The GP/DC should initially review the notes without the patient and at that stage the following scenarios may emerge:
 - Patient has had Trimipramine as an acute prescription
 - Patient has Trimipramine on repeat prescription but does not seem to have it regularly
 - Patient has Trimipramine regularly on repeat prescription
9. The GP/DC will have to take an action that is appropriate regarding any one of the above scenarios.
10. Generally the information in this SOP is relevant to a situation where the aim is to de-prescribe Trimipramine or switch treatment to a more suitable alternative in patients who take Trimipramine regularly. In such a situation it is envisaged that the GP/DC will see the patient face to face or at least have a telephone conversation.
11. The choice of alternative anti-depressant should be made on an individual patient basis and will depend on factors such as suicidal risk, concomitant medication, the need for sleep etc. See NICE Clinical Knowledge Summaries, NICE CG90, the BNF and relevant summary of product characteristics for further information.
12. Once a decision to de-prescribe Trimipramine has been agreed with the patient, the GP/DC will have to make sure that arrangements are in place for the GP/clinician to issue prescriptions for the reducing doses of Trimipramine and for the practice staff to notify the patients; Or
13. Once a decision to change the treatment has been agreed with the patient, the GP/DC will have to make sure that arrangements are in place for the GP to issue prescriptions for the alternative drug that is appropriate for the individual patient and for the practice staff to notify the patients. There might also be situations where cross tapering occurs i.e. when the patient is being tapered off Trimipramine and an alternative medication is being started.
14. There will be a need for the patient to be able to contact the GP/DC to report progress and to discuss any issues.
15. If at any point in the review process a case of prescribing is found that poses a significant safety concern for the patient then that should be brought to the GP's attention as soon as it is practical to do so.
16. The end point for the review will be when the patient can be transferred back to the GP or another appropriate clinician for ongoing care.
17. Throughout the process appropriate entries (including agreement from GP regarding any actions) should be made on the medical record/clinical system. This will provide the audit trail and therefore there is no need to have hard copies of any patient details.
18. Note there are no audit sheets or patient letters for this review as the advice and communication must be tailored to patient's requirements.
19. The GP/DC should also liaise with the patient's community pharmacist and explain the plan.

20. Record saving/intervention on MedOptimise under designated practice and QIPP work stream area. **Ensure no patient identifiable information is entered onto MedOptimise.**

Note: the remainder of the SOP provides general information to support the DC in de-prescribing Trimipramine or switching it to an alternative treatment

Learning from local audits

Previously, in North Staffordshire and Stoke-on-Trent patients taking Trimipramine were reviewed. Generally these patients had been on Trimipramine for many years and were not always sure why they were on treatment. Some patients reported that they were taking the drug for a combination of symptoms which could be linked to anxiety, depression and insomnia.

Thus the initial discussion between the GP/DC and the patient needs to focus on how the patient feels about their treatment in terms of indication, effectiveness, any side-effects and what they would like to do going forward. It is important to point out to the patient that the adverse effects from Trimipramine become more problematic as the patient gets older. For example, effects on cognitive function, cardiac conduction, accommodation, detrusor activity and peristalsis may become much more troublesome in older age. The GP/DC should emphasize the clinical reasons for changing treatment as well as the cost benefit.

After discussion with the patient the potential actions may be:

4. To de-prescribe
5. Consider switch to Sertraline
6. Consider switch to an alternative appropriate antidepressant
7. Consider seeking specialist support – if patient is very concerned about stopping or changing treatment then the main course of action would be GP referral to a specialist.

In situations where Trimipramine will be either de-prescribed or switched to another drug, the DC should make appropriate arrangements with the GP, practice staff and the patient on how Trimipramine will be stepped down, how an alternative drug will be introduced and how the patient will get the relevant prescriptions. A tapering schedule will should be provided for the patient and documented in their clinical record indicating how the dose has been tapered down and an alternative medication added if required. There will be a need to forewarn the local pharmacy so that tablets of appropriate strength are ore ordered and stocked at the pharmacy.

This review work will require several face to face or telephone consultations with the patient to assess how they are progressing. It will also take a considerable amount of time before a particular case can be closed and then the patient can be followed up as per routine practice procedures. NICE Clinical Knowledge Summaries contains information on how to assess a patient with depression at review <https://cks.nice.org.uk/topics/depression/management/ongoing-management/>. This includes the use of a validated assessment tool to monitor the patients' progress⁵.

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The use and application of this SOP does not override the individual responsibility of health care professionals to make decisions appropriate to local need and circumstances of individual patients (in consultation with the patient and/or guardian or carer).

De-prescribing Trimipramine

De-prescribing should only be attempted if history of severe depression has been ruled out. If there is history of longstanding depression then the options (within this protocol) are switching to Sertraline or referring to the secondary care provider.

For patients who have started Trimipramine relatively recently then it should be remembered that any antidepressant treatment should continue for at least six months after remission of a depressive episode increased to at least two years for those at risk of relapse. In such scenarios also the options within this protocol are switching to Sertraline or referring to secondary care

In cases where the patient is taking Trimipramine but is sure that they never took the medication for depression and are not certain about how the treatment benefits them currently then de-prescribing can be attempted. The following de-prescribing schedule is taken from PrescQIPP Bulletin B204 (December 2017)³ on Trimipramine:

	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

The patient should be able to contact the DC/GP with any queries or problems that they are experiencing whilst stepping down the dose of treatment.

Switching treatment from Trimipramine to Sertraline

For patients who have depression with more anxiety component and who do not require a sedative effect then Trimipramine could potentially be switched to Sertraline. The patient should be given information about Sertraline during the initial discussion. If the patient does not want to take Sertraline based on the information presented or if they have used the drug in the past and did not continue for whatever reason then the matter should be discussed with the GP. If another drug is suggested by the GP then the DC will have to ensure that they have checked the necessary information on how Trimipramine can be switched to the alternative drug. The choice of alternative anti-depressant should be made on an individual patient basis taking into account factors such as suicidal risk, compliance and concomitant medication, the impact on libido and sedative effects of the medication. Reference should be made to the BNF, up to date relevant NICE guidelines, individual DLCV: Trimipramine SOP, Version 2, Nov 2021

drug summary of product characteristics and the local formulary when deciding on the choice of alternative anti-depressant. It must be noted that caution is required when switching antidepressants as there are no clear guidelines on how to do this⁶. Some alternative antidepressant drug options that could be considered include:

- Citalopram or Escitalopram especially in cases where patient has associated anxiety or panic disorders. Check patient is not on concomitant drugs that can increase QT interval (see MHRA guidance on Citalopram and Escitalopram (QT interval prolongation) <https://www.gov.uk/drug-safety-update/citalopram-and-escitalopram-qt-interval-prolongation?UNLID=772070123202196112810>⁷
- Fluoxetine – useful where compliance is a problem as it has a long half-life.
- Mirtazapine – can be considered where an SSRI is not suitable. It has sedative effects where this may be desirable. Further information on switching to Mirtazapine is present later in this SOP. Please note it is associated with a risk of blood disorders – see BNF⁸

Do not switch to:

- Dosulepin^{2,4}. This medicine is associated with an increased cardiac risk and toxicity in overdose⁴.
- Amitriptyline – increased risk of toxicity in overdose⁸.
- Avoid Paroxetine due to the side effect profile of this medicine and that it interacts with many medicines⁸. Higher risk of withdrawal effects⁹.
- Venlafaxine – Toxicity in overdose.

Please also refer to relevant NICE guidelines, the BNF, individual drug summary of product characteristics and relevant CKS (Clinical Knowledge Summaries) guidance. APPENDIX A contains information from Clinical Knowledge Summaries (CKS) on switching from a TCA to an alternative anti-depressant.

The following switching protocol is taken from PrescQIPP Bulletin B204 (December 2017)³ on Trimipramine:

	Medication	Current daily dose	Week one	Week two	Week three	Week four
Switching from trimipramine 150mg daily dose to sertraline (minimum effective dose)	Trimipramine	150mg daily	75mg daily	50mg daily	25mg daily	Stop
	Sertraline	0mg daily	25mg daily	50mg daily	50mg daily	If necessary, start to titrate sertraline up by 50mg at intervals of one week until minimum effective dose reached. Maximum daily dose 200mg

	Medication	Current daily dose	Week one	Week two	Week three	Week four
Switching from trimipramine 100mg daily dose to sertraline (minimum effective dose)	Trimipramine	100mg daily	50mg daily	25mg daily	10mg daily	Stop
	Sertraline	0mg daily	25mg daily	50mg daily	50mg daily	If necessary, start to titrate sertraline up by 50mg at intervals of one week until minimum effective dose reached. Maximum daily dose 200mg
Switching from trimipramine 75mg daily dose to sertraline (minimum effective dose)	Trimipramine	75mg daily	35mg daily	20mg daily	10mg daily	Stop
	Sertraline	0mg daily	25mg daily	50mg daily	50mg daily	If necessary, start to titrate sertraline up by 50mg at intervals of one week until minimum effective dose reached. Maximum daily dose 200mg

Please refer to PrescQIPP bulletin B204 for further information.

Switching treatment from Trimipramine to Mirtazapine

Patients who are relying on Trimipramine to help sleep and are reluctant to be without any treatment then Mirtazapine can be offered as an alternative. As in above protocol reduce dose of Trimipramine over 3 to 4 week period – the exact dose is dependent on starting dose of Trimipramine as explained above. Introduce Mirtazapine at a dose of 15mg daily and review patient after 4 weeks before making any further changes to the dose. Note that the sedative effect of Mirtazapine is more pronounced at lower doses – at a dose of 45mg daily Mirtazapine has a stimulant effect.

** The term 'DC (Designated Clinician)' refers to a suitably trained GP or non-medical prescriber at the practice who has been assigned, by the GP Prescribing Lead of the practice, to authorise and oversee work at the practice in accordance with this SOP.*

References and resources

1. Drug Tariff online August 2021. <https://www.drugtariff.nhsbsa.nhs.uk/#/00805984-DC/DC00805981/Home> <accessed Aug 2021>
2. Depression in adults: recognition and management. Clinical guideline (CG90). Published 28 October 2009. <https://www.nice.org.uk/guidance/cg90> <accessed 06.09.2021>
3. PrescQIPP Bulletin on switching Trimipramine to Sertraline or Imipramine. Bulletin B204. December 2017
4. NHSE guidance on items which should not be primarily prescribed in primary care: guidance for CCGs. <https://www.england.nhs.uk/publication/items-which-should-not-be-routinely-prescribed-in-primary-care-guidance-for-ccgs/> <accessed 06.09.2021>
5. Clinical Knowledge Summaries (CKS) <https://cks.nice.org.uk/topics/depression/management/ongoing-management/> <accessed 06.09.2021>
6. Taylor, D. and Barnes, T.R.E., Young, A.H (Eds.) (2018) The Maudsley prescribing guidelines in psychiatry. 13th edn. Chichester: Wiley Blackwell.
7. Drug Safety Update <https://www.gov.uk/drug-safety-update/citalopram-and-escitalopram-gt-interval-prolongation?UNLID=772070123202196112810> <accessed 06.09.2021>
8. BNF online September 2021 <https://bnf.nice.org.uk/treatment-summary/antidepressant-drugs.html> <accessed 06.09.2021>
9. North Staffordshire Joint Formulary <https://www.northstaffordshirejointformulary.nhs.uk/chaptersSubDetails.asp?FormularySec>

[tionID=4&SubSectionRef=04.03.03&SubSectionID=A100&drugmatch=1122#1122](#) <accessed 06.09.2021>

10. UKMi October 2019: How do you switch between tricyclic, SSRI and related antidepressants?
https://www.sps.nhs.uk/wp-content/uploads/2019/09/UKMI_QA_How-do-you-switch-between-MAOI-SSRI-TCA-or-related-ADs_update_April-2019.pdf

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The use of this document is the responsibility of the user, and the CCG will bear no liability for its use.

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APPENDIX A

CKS information on switching from a TCA to an alternative antidepressant. Visit <https://cks.nice.org.uk/topics/depression/prescribing-information/switching-antidepressants/> for further details:

Switching from:	Switching to:				
	TCA (except clomipramine)	SSRI (citalopram, escitalopram, paroxetine or sertraline)	SNRI (duloxetine, venlafaxine)	Fluoxetine	Mirtazapine
TCA (except clomipramine)	Direct switch possible	Gradually reduce the dose of TCA to 25–50 mg daily [SPS, 2019c] or half the usual dose [Taylor, 2018]. Start SSRI then slowly withdraw TCA over next 5–7 days [SPS, 2019c]	Cross-taper cautiously starting with low dose SNRI	Halve dose of TCA, add fluoxetine and then slowly withdraw TCA	Cross-taper cautiously