PrescQIPP Community Interest Company

Trimipramine

This is one of a number of bulletins providing further information on medicines that should be given a low priority, are poor value for money, suitable for self care or for which there are safer more suitable alternatives. This guidance will support Clinical Commissioning Groups (CCGs) in taking action on items that should not routinely be prescribed in primary care or on the NHS.

Further bulletins, including the overarching low value medicines bulletin, are available on the PrescQIPP website at: https://www.prescqipp.info/droplist/projectsection/default1/the-prescqipp-drop-list

Recommendations

- Tricyclic antidepressants (TCAs) should not be used first line for the treatment of depression. Selective Serotonin Reuptake Inhibitors (SSRIs) are recommended by NICE as they are equally effective and have a more favourable risk-benefit ratio.
- Where a TCA is indicated in accordance with NICE, trimipramine should not be prescribed as it is not considered to be cost effective for prescribing on the NHS.
- Patients already being prescribed trimipramine should be reviewed in line with the current NICE clinical guidance and supporting resources accompanying this bulletin.
- Ongoing prescribing of antidepressants should be reviewed after six months or two years depending on the person's risk of relapse.
- If trimipramine is being prescribed for an unlicenced indication (e.g. anxiety, neuropathic pain, fibromyalgia or insomnia) consider discontinuation or switching treatment to a more appropriate alternative in collaboration with an appropriate specialist.

Introduction

Trimipramine is a tricyclic antidepressant (TCA) indicated for the treatment of depressive illness, particularly where sedation is required. However, TCAs are not recommended as a first line treatment option in adults with depression by NICE and they are not recommended at all for children and adolescents (aged under 18 years).[1,2] SSRIs are preferred as they have less side effects, are safer in overdose, require less dosage titration and instead of, need only once daily dosing which may mean better patient adherence.[1,3]

Where a TCA is indicated, as set out by NICE,[1] trimipramine does not represent a cost-effective choice of TCA as it has been subjected to excessive price inflation. More cost effective products are available. The cost per 28 days for trimipramine is currently £380 (based on a maintenance dose of 100mg daily).[4] The comparative cost of an alternative TCA, imipramine, is £2.91 (based on a maintenance dose of 75mg daily).[4] Where an SSRI would be more appropriate, sertraline costs is £1.21 for a 28 day supply (based on a maintenance dose of 100mg daily).[4]

Background

Depression is a broad and heterogenous disease, which can be distressing and disabling. Depression often has a remitting and relapsing course, and symptoms may persist between episodes.[1] Where possible, the key goal of an intervention should be complete relief of symptoms (remission), which is associated with better functioning and a lower likelihood of relapse.[1]

Antidepressant drugs should not be used to treat persistent subthreshold depressive symptoms or mild depression because the risk–benefit ratio is poor.[1] They should be considered for people with a past history of moderate or severe depression or initial presentation of subthreshold depressive symptoms that have been present for a long period (typically at least two years) or subthreshold depressive symptoms or mild depression that persist(s) after other interventions.[1]

For people with moderate or severe depression, a combination of antidepressant medication and a high-intensity psychological intervention is recommended.[1] For relapse prevention, a person who has benefited from taking an antidepressant should be encouraged to continue medication for at least six months after remission of an episode of depression as this greatly reduces the risk of relapse.[1]

If a person is considered at risk of relapse, then antidepressants should be continued for at least two years.[1] People are considered to be at risk of relapse if they have had two or more episodes of depression in the recent past, during which they experienced significant functional impairment OR they have other risk factors for relapse such as residual symptoms, multiple previous episodes, or a history of severe or prolonged episodes of inadequate response OR the consequences of relapse are likely to be severe (for example, suicide attempts, loss of functioning, severe life disruption, and inability to work).[1]

The recommended first line treatment choice is a generic SSRI because they are equally as effective as other antidepressants and have a more favourable risk-benefit ratio.[1] Tricyclic antidepressants should NOT be prescribed for children and adolescents (aged under 18 years) as the risks significantly outweigh the benefits.[2]

Where possible, choice of antidepressant drug should be matched to individual patient requirements.[1] Consideration should be given to both short-term and long-term effects, additional physical health disorders, overdose risk, previous exposure, tolerance and response, concurrent medication and patient preference.[5]

Reviewing prescribing – stopping or switching

A trial discontinuation of trimipramine should be considered if long-term maintenance is no longer considered necessary. Evaluation of this should take into account comorbid conditions, risk factors for relapse and severity and frequency of episodes of depression. Antidepressant treatment should be continued for at least six months after remission of a dose of depression, increased to at least two years for those at risk of relapse as defined above.[1]

Where antidepressant treatment is still indicated, SSRIs are usually preferred due to their more favourable risk/benefit profile.[1] Choice of treatment should take into account the duration of the episode of depression and the trajectory of symptoms, previous course of depression and response to treatment, likelihood of adherence to treatment and any potential adverse effects and the person's treatment preferences and priorities.[1]

If an SSRI represents a clinically appropriate alternative for the individual patient, then a managed switch from trimipramine to sertraline should be tried (as detailed below).

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 non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin.[1]

If an SSRI isn't appropriate and an alternative TCA would be a more suitable alternative, a managed switch to imipramine is recommended as it is less sedative, cost effective and less cardiotoxic in overdose (see suggested switching regimens). Bear in mind that TCAs are associated with the greatest risk in overdose of all antidepressant classes and an increased likelihood of the person stopping treatment because of side effects.[1]

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.[6] 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.[6] When changing from one antidepressant to another, abrupt withdrawal should usually be avoided. Any switching should be carried out with the appropriate cross-tapering regimen and patients should be very carefully monitored.[6] The tables below provide some additional guidance on how to manage this. However, the speed of cross-tapering is best judged by individual patient tolerability. If patients are not tolerating the change, cross-taper more slowly. It should be noted that there are no clear guidelines on switching antidepressants, so caution is required.[5]

Stopping trimipramine[3,5,6]

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	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

Switching from trimipramine to sertraline[3,5,6]

Start by halving the dose of trimipramine then add sertraline and cross-taper over four weeks. Doses below are represented as total daily doses and do not reflect frequency. The lowest effective dose of the replacement antidepressant should be used and adjusted individually according to the patient's response.

	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

Switching from trimipramine to imipramine[3,5,6]

Cross tapering between two different tricyclic antidepressants should be done cautiously. Please note, doses below are represented as total daily doses and do not reflect frequency. The lowest effective dose of the replacement antidepressant should be used and adjusted individually according to the patient's response. The usual maintenance dose of imipramine is 50-100mg daily.

	Medication	Current daily dose	Week one	Week two	Week three	Week four	Week five
Switching from trimipramine 150mg daily dose to imipramine (minimum effective dose)	**Trimipramine**	150mg daily	100mg daily	75mg daily	50mg daily	25mg daily	Stop
	Imipramine	0mg daily	50mg daily	75mg daily	100mg daily	125mg daily	If needed dose can be taken to 150mg-200mg. Maintain this dose until improvement is seen then gradually reduce to a maintenance dose of 50mg to 100mg[7]

	Medication	Current daily dose	Week one	Week two	Week three	Week four	Week five
Switching from trimipramine 100mg daily dose to imipramine (minimum effective dose)	**Trimipramine**	100mg daily	75mg daily	50mg daily	25mg daily	Stop	
	Imipramine	0mg daily	25mg daily	50mg daily	75mg daily	100mg daily	If needed dose can be taken to 150mg-200mg. Maintain this dose until improvement is seen then gradually reduce to a maintenance dose of 50mg to 100mg[7]

	Medication	Current daily dose	Week one	Week two	Week three
Switching from trimipramine 75mg daily dose to imipramine (minimum effective dose)	**Trimipramine**	75mg daily	50mg daily	25mg daily	Stop
	Imipramine	0mg daily	25mg daily	50mg daily	75mg If needed dose can be taken to 150mg-200mg. Maintain this dose until improvement is seen then gradually reduce to a maintenance dose of 50mg to 100mg[7]

Withdrawal effects

Withdrawal effects may occur within five days of stopping treatment with antidepressant drugs.[6] 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.[6]

Common symptoms:[5]

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

Occasionally:[5]

- 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.[5] 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.[5]

Costs

The table below shows the cost of trimipramine compared to other medicines used for the treatment of depression in primary care. The prices are from the September 2017 Drug Tariff.[4]

Drug	Class of antidepressant	Usual maintenance dose	Cost per 28 tablets or capsules (£)
Trimipramine 10mg tablets	TCA	75-150mg daily	£179.15
Trimipramine 25mg tablets	TCA	75-150mg daily	£200.50
Trimipramine 50mg capsules (Zentiva®)	TCA	75-150mg daily	£190.00
Imipramine 10mg tablets	TCA	50-200mg daily	0.87
Imipramine 25mg tablets	TCA	50-200mg daily	0.88
Sertraline 50mg tablets	SSRI	50-200mg daily	0.92
Sertraline 100mg tablets	SSRI	50-200mg daily	1.10

In England and Wales, over £17.9 million is currently being spent on trimipramine preparations in the course of a year (ePACT July 2017 to September 2017). Stopping or reducing the use of trimipramine in favour of a more cost-effective alternative, **has the potential to release savings of up to £17.9 million which equates to £30,711 per 100,000 patients.** There will be a minimal offset of the savings if a switch to an alternative product is appropriate.

Full details of savings available in the data pack: https://pdata.uk/views/B204_Trimipramine/Bulletindata?%3Aiid=2&%3AisGuestRedirectFromVizportal=y&%3Aembed=y

As with all switches, individual patient circumstances need to be borne in mind. However, with guidance on switching antidepressant treatment, support from your local CCG prescribing teams and the input of relevant specialist teams, where appropriate, it is hoped that GPs will participate in realising this saving.

References

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Additional PrescQIPP resources

 Briefing

 Audits, patient letters and information

Available here: https://www.prescqipp.info/b204-trimipramine/category/416-trimipramine

 Data pack

Available here: https://pdata.uk/views/B204_Trimipramine/Bulletindata?%3Aiid=2&%3AisGuestRedirectFromVizportal=y&%3Aembed=y

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