Trimipramine Guidance: Stopping or switching to alternative therapy

The NHS England and NHSCC led clinical working group developed guidelines regarding a list of 18 products which they considered to be ineffective, unnecessary, inappropriate or unsafe for prescription on the NHS. Trimipramine was identified as a Product which was clinically effective but where more cost-effective products are available (this includes products that have been subject to excessive price inflation).

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.

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 switching to citalopram, prescribers are reminded, that due to the risk of dose-related QTc prolongation, the maximum dose for adults is 40mg daily (20mg daily for over 65s and in patients with renal impairment)[8]. Coadministration of citalopram [or escitalopram] with medicines that prolong the QT interval is therefore contraindicated. Caution is also advised in patients taking concomitant medications known to increase plasma levels of citalopram [or escitalopram], and this may necessitate SSRI dose reduction.

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]

Trimipramine Withdrawal and Cross Tapering Guidelines

Withdrawal effects may occur within 5 days of stopping treatment with antidepressant drugs; they are usually mild and self-limiting, but in some cases may be severe. The risk of withdrawal symptoms is also increased if the antidepressant is stopped suddenly after regular administration for 8 weeks or more.

Common symptoms:[5]

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

Occasionally:[5]

Movement disorders
Mania
Cardiac arrhythmias

The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). When changing from one antidepressant to another, abrupt withdrawal should usually be avoided. Cross-tapering is preferred, in which the dose of the ineffective or poorly tolerated drug is slowly reduced while the new drug is slowly introduced. **The speed of cross-tapering is best judged by monitoring patient tolerability. No clear guidelines are available, so caution is required. If patients are not tolerating, cross taper more slowly.** Maximum dose is dependent on individual patient's response. 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.
Trimipramine may be changed to imipramine as a like for like replacement but alternatively an SSRI or Mirtazapine may be used.

Trimipramine to Imipramine

Tricyclics should be Cross-tapered from one to another cautiously. **Doses below are expressed as total daily dose and do not reflect the frequency. See BNF and product specification for maximum daily dose and frequency (BNF doses may differ from SPC). The lowest effective dose should be used and adjusted individually to patient's response.**

Reducing from Trimipramine 150mg

Medication	Current total daily dose	Week One	Week Two	Week Three	Week Four	Week Five	Week Six	Week Seven	Week Eight	Notes
Trimipramine	**150mg**	**125mg**	**100mg**	**75mg**	**50mg**	**25mg**	**20mg**	**10mg**	**0mg**	
Imipramine	**0mg**	**50mg**	**50mg**	**100mg**	**100mg**	**125mg**	**125mg**	**150mg**	**150mg**	**Usual maintenance dose 50-100mg**

Reducing from Trimipramine 100mg

Medication	Current total daily dose	Week One	Week Two	Week Three	Week Four	Week Five	Week Six	Notes
Trimipramine	100mg	75mg	50mg	25mg	20mg	10mg	0mg	
Imipramine	0mg	25mg	50mg	75mg	100mg	100mg	100mg	Usual maintenance dose 50-100mg

Reducing from Trimipramine 75mg

Medication	Current total daily dose	Week One	Week Two	Week Three	Week Four	Notes
Trimipramine	75mg	50mg	25mg	10mg	0mg	
Imipramine	0mg	25mg	50mg	100mg	100mg	Usual maintenance dose 50-100mg

Trimipramine to SSRI

The dose of tricyclics must be halved before cross-tapering to SSRIs. **Doses below are expressed as total daily dose and do not reflect the frequency. See BNF and product specification for maximum daily dose and frequency (BNF doses may differ from SPC). The lowest effective dose should be used and adjusted individually to patient's response.**

Reducing from Trimipramine 150mg

Medication	Current total daily dose	Week One	Week Two	Week Three	Week Four	Week Five	Week Six	Week Seven	Week Eight	Notes
Trimipramine	150mg	75mg	60mg	50mg	40mg	30mg	20mg	10mg	0mg	
Citalopram	0mg	10mg	10mg	20mg	20mg	30mg	30mg	30mg/ 40mg	30mg/ 40mg	Maximum of 40 mg a day [20mg daily in over 65s and patients with hepatic impairment]; BNF maximum dose may differ from SPC
Fluoxetine	0mg	10mg	10mg	20mg	20mg	30mg	30mg	40mg	40mg	Maximum of 60mg.
Paroxetine	0mg	10mg	10mg	20mg	20mg	30mg	30mg	40mg	40mg	Maximum of 50mg; BNF maximum dose may differ from SPC
Sertraline	0mg	25mg	25mg	50mg	50mg	75mg	75mg	100mg	100mg	Maximum of 200 mg.

Reducing from Trimipramine 100mg

Medication	Current total daily dose	Week One	Week Two	Week Three	Week Four	Week Five	Notes
Trimipramine	100mg	50mg	30mg	20mg	10mg	0mg	
Citalopram	0mg	10mg	10mg	20mg	30mg/40mg	30mg/40mg	Maximum of 40 mg a day; BNF maximum dose may differ from SPC
Fluoxetine	0mg	10mg	10mg	20mg	30mg	40mg	Maximum of 60mg.
Paroxetine	0mg	10mg	10mg	20mg	30mg	40mg	Maximum of 50mg; BNF maximum dose may differ from SPC
Sertraline	0mg	25mg	50mg	75mg	100mg	150mg	Maximum of 200 mg.

Reducing from Trimipramine 75mg

Medication	Current total daily dose	Week One	Week Two	Week Three	Week Four	Week Five	Notes
Trimipramine	75mg	30mg	30mg	20mg	10mg	0mg	
Citalopram	0mg	10mg	10mg	20mg	30mg/ 40mg	30mg/ 40mg	Maximum of 40 mg a day; BNF maximum dose may differ from SPC
Fluoxetine	0mg	10mg	10mg	20mg	30mg	40mg	Maximum of 60mg.
Paroxetine	0mg	10mg	10mg	20mg	30mg	40mg	Maximum of 50mg; BNF maximum dose may differ from SPC
Sertraline	0mg	25mg	50mg	75mg	100mg	150mg	Maximum of 200 mg.

Contact details for advice and support

North East London Foundation Trust	Access, assessment and brief intervention team
Redbridge	0300 300 1570 (option 1)
Havering	0300 300 1570 (option 2)
Barking & Dagenham	0300 300 1570 (option 3)

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