TRAZODONE DEPRESCRIBING

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Summary

Sedative drugs other than hypnotics are not recommended for the management of insomnia. There is insufficient evidence to support their use, and the potential for adverse effects is significant.

Trazodone should not be used first line for depression. Selective Serotonin Reuptake Inhibitors (SSRIs) are recommended by NICE as they are equally effective and have a more favourable risk-benefit ratio.

Trazodone should not be used first line for anxiety in dementia (local guidance positions mirtazapine first line). Trazodone liquid is very expensive (120ml of liquid costs £109.20, compared to £7.11 for a box of capsules). Trazodone should be used after mirtazapine has been trialled/considered, and the liquid should only be used for those on unusual doses where a capsule is unavailable (i.e. 25mg OD/ 75mg OD), or where the patient has swallowing difficulties.

This document explores amending trazodone in patients where the medication is being used inappropriately.

Background

In the RightCare reports, "Commissioning for Value Mental health and dementia pack", trazodone prescribing highlighted Nottingham West and Rushcliffe as outliers compared to similar sized CCGs across the country.

NICE CG90 (Depression in adults) recommends, for people with persistent depressive symptoms or mild to moderate depression who have not benefited from a low-intensity psychosocial intervention;

- an antidepressant (normally a selective serotonin reuptake inhibitor [SSRI])

Trazodone is referenced in CG91 – *Depression in adults with a chronic physical health problem: recognition and management*, in the following scenarios;

> 1.5.2.6 Do not normally offer SSRIs to patients taking non-steroidal anti-inflammatory drugs (NSAIDs) because of the increased risk of gastrointestinal bleeding. Consider offering an antidepressant with a lower propensity for, or a different range of, interactions, such as mianserin, mirtazapine, moclobemide, reboxetine or trazodone.
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> 1.5.2.9 Use SSRIs with caution in patients taking aspirin. When aspirin is used as a single agent, consider alternatives that may be safer, such as trazodone, mianserin or reboxetine.
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> 1.5.2.12 Do not offer SSRIs to patients receiving 'triptan' drugs for migraine. Offer a safer alternative such as mirtazapine, trazodone, mianserin or reboxetine.
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> 1.5.2.13 Do not normally offer SSRIs at the same time as monoamine oxidase B (MAO-B) inhibitors such as selegiline and rasagiline. Offer a safer alternative such as mirtazapine, trazodone, mianserin or reboxetine.

There is some evidence to suggest that trazodone is more effective in those suffering from insomnia, although it should be noted that in these cases 50mg OD is all that is necessary to block the binding sites responsible for the hypnotic effect – and this is not a licensed indication for the medication.

A recent meta-analysis found that of the 21 reviewed antidepressants, trazodone was among the least effective and least well tolerated when compared with placebo and other antidepressants.

Locally on the Nottinghamshire Joint Formulary the anti-depressant Trazodone is classified as GREEN, and is recommended "Second line after mirtazapine in the treatment of severe anxiety in dementia patients in the context of behavioural and psychological symptoms of dementia".

The medication appears to be used to some extent in the elderly as per the local Nottinghamshire guidelines "*Managing Behaviour and Psychological Problems in Patients with Diagnosed or Suspected Dementia in Primary and Secondary Care"*. This recommended usage is as per licensed indication of the medication;

- 2nd line (to mirtazapine) in alzheimer's for severe anxiety (25mg starting dose, maximum 150mg/day).

Example audit – Nottingham West CCG

Data was collected in February 2018 on all patients currently prescribed trazodone in a practice in Nottingham West CCG. The practice was chosen due to irregularly high prescribing levels, and was deemed a feasible representation of the high prescribing figures described in the NHS RightCare document addressing mental health and dementia care.

121 patients were identified, with 81 deemed appropriate for review in the audit.

Two standards were audited;

- *Patients prescribed as per the local APC guidance (for use in patients with dementia and severe anxiety)*
- *Patients prescribed as per NICE CG91*

Compliance with APC guidance was found to be 75% (n=4)
Compliance with NICE guidance was found to be 5% (n=77)

Example audit – Mansfield & Ashfield CCG

Data was collected in May 2018 to assess practice with Trazodone in a practice in Mansfield and Ashfield CCG. The site was chosen on recommendation of the medicines management team who stated practice here was representative of the region.

74 patients were identified, with 46 deemed appropriate for the audit.

Two standards were audited;

- *Patients prescribed as per the local APC guidance (for use in patients with dementia and severe anxiety)*
- *Patients prescribed as per NICE CG91*

Compliance with APC guidance was found to be 31% (n=24)

Compliance with NICE guidance was found to be 14% (n=22)

This document was designed to address the trends identified in these audits, and should be used as such to improve practice with trazodone.

Amending prescribing – stopping, switching where medication inappropriately prescribed

When to amend trazodone

Current standards state when the following standards are not adhered to, the patient should be reviewed for switching to a more appropriate medication;

- **2nd line (to mirtazapine) in alzheimer's for severe anxiety (25mg starting dose, maximum 150mg/day).**
- **Where SSRIs are contraindicated in patients using aspirin (suggested alternative)**
- **Where a patient is using a triptan (mirtazapine and trazodone suggested alternatives**
- **Where patient is using MAO-B (mirtazapine and trazodone suggested alternatives)**

In practice, the audits carried out indicated the medication was frequently prescribed inappropriately for the

following;

- **Insomnia patients**
- **For headache/pain (Neuropathic pain guidance – Notts APC)**
- **Those using diazepam/Z drugs and trazodone for sleep**
- **Patient expressed that they want to stop**
- **Suicidal ideation**

These patients should be the main focus of trazodone de-prescribing. The patient should be involved in the decision on whether to stop or switch to a more efficacious (and cost effective) alternative.

A trial discontinuation of antidepressants should be considered if long-term maintenance is no longer considered necessary. Evaluation should take into account comorbid conditions, risk factors for relapse and severity and frequency of depression.
Antidepressant treatment should be continued for at least six months after remission of an episode of depression, increased for those at risk of relapse to two years.

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 or prolonged episodes or of inadequate response
- the consequences of relapse are likely to be severe (for example, suicide attempts, loss of functioning, severe life disruption, and inability to work).

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. Where antidepressant treatment is still indicated, SSRIs are preferred due to their more favourable risk/benefit profile. The first choice SSRI in Nottinghamshire is sertraline, and a table for switching from trazodone to sertraline is included below.

Current NICE guidance states mirtazapine as an alternative to SSRIs, similar to trazodone. It should be noted that the side effect profile of mirtazapine makes it a suitable alternative to SSRIs, and a common side effect of the medication is somnolence – which may make it appropriate in those using trazodone for such effects. A table describing switching from trazodone to mirtazapine is included below.

Patient choice is important when switching medications. They should be aware of common side effects of the medications where relevant. For example, sertraline is non-sedating and weight neutral while mirtazapine is sedating and carries higher likelihood of weight gain.

The patient should be made aware of information available that may answer questions they have on their medication. A good resource is;
http://www.choiceandmedication.org/nottinghamshirehealthcare/condition/depression/

The following tables explain the stopping/switching process. Due to the risk of discontinuation syndrome with sudden cessation of therapy with antidepressants, discontinuation and switching must be managed carefully. 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 cross-tapering regimen and patients should be very carefully monitored. However, the speed of cross-tapering is best judged by individual patient tolerability. If patients are not tolerating the change, cross-taper more slowly (a patient that has been using trazodone for many years may require cross tapering over several months). It should be noted that there are no clear guidelines on switching antidepressants, so caution is required. The following advice has been interpreted from Maudsley and MIMS guidance.

How to stop

The Maudsley prescribing guide recommends that trazodone is stopped gradually over 4 weeks. This timeframe can be expanded if withdrawal symptoms emerge.

	Current dose	Week one	Week two	Week three	Week four
Reducing from 300mg daily dose	300mg/day	200mg/day	100mg/day	50mg/day	Stop
Reducing from 150mg daily dose	150mg/day	100mg/day	50mg/day	Stop	Stop
Reducing from 50mg daily dose	50mg/day	Stop	Stop	Stop	Stop

Advise patients that discontinuation symptoms may occur on stopping the medication. These should be mild and self-limiting after about a week, but can be severe, particularly if the drug is stopped abruptly. Education is the strongest tool here – please see the section below on withdrawal effects.

If a patient complains of worsening insomnia, refer to NICE CKS on treating insomnia. Good sleep hygiene is most important (see "sleep hygiene advice"). Remember, pharmacological therapy is generally **not recommended** and where it is, **should not routinely be prescribed beyond 2 weeks and never longer than 4 weeks**.

How to switch

Patient should be switched to appropriate first line choice as per NICE CG90 or NICE CG91.

In Nottinghamshire the first choice antidepressant is sertraline, but if the patient has contraindications to this there are other alternatives (of which mirtazapine is a strong candidate) - Nottinghamshire Formulary.

Sertraline is a non-sedative anti-depressant, while a common side effect of mirtazapine is sedation.

The Maudsley prescribing guidelines in psychiatry recommend the following* when switching from TCAs to another antidepressant

SSRIs	Fluoxetine	Mirtazapine	SNRIs (Duloxetine, Venlafaxine)
Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously	Cross-taper cautiously

*Reference materials recommend "cautious cross-tapering". In this case the speed of the cross-tapering should be judged by monitoring the tolerability of the switch by the individual patient. NICE guidance recommends a 4-week reduction period when removing an anti-depressant, longer in some cases. The addition of another medication can help mitigate side effects.

How to switch to sertraline

A cautious approach to cross-tapering would be to do the following (following the logic of reducing the dose by half, then gradually increase the sertraline dose), reaching minimum effective dose by the end of a month;

	Medication	Current dose	Week one	Week two	Week three	Week four
Switching from 300mg trazodone to sertraline (minimum daily dose)	Trazodone	300mg/day	200mg/day	100mg/day	50mg/day	Stop
	Sertraline	0mg/day	0mg/day	25mg/day	50mg/day	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 150mg trazodone to sertraline (minimum daily dose)	Trazodone	150mg/day	100mg/day	50mg/day	Stop	Stop
	Sertraline	0mg/day	25mg/day	25mg/day	50mg/day	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 50mg trazodone to sertraline (minimum daily dose)	Trazodone	50mg/day	Stop	Stop	Stop	Stop
	Sertraline	0mg/day	25mg alternate days	25mg/day	50mg/day	If necessary, start to titrate sertraline up by 50mg at intervals of one week until minimum effective dose reached. Maximum daily dose 200mg

- Remember SSRIs are associated with an increased risk of bleeding, so check for and consider prescribing a gastro-protective drug in older adults who are also using NSAIDs and/or aspirin. The first line proton pump inhibitors [PPIs] on Nottinghamshire formulary are lansoprazole or omeprazole.

How to switch to mirtazapine

A cautious approach to cross-tapering would be to do the following (following the logic of reducing the dose by half, then introducing the mirtazapine cautiously), reaching minimum effective dose by the end of a month. Mirtazapine can be titrated further from this point.

	Medication	Current dose	Week one	Week two	Week three	Week four
Switching from 300mg trazodone to mirtazapine (minimum daily dose)	Trazodone	300mg/day	200mg/day	100mg/day	50mg/day	Stop
	Mirtazapine	0mg/day	0mg/day	0mg/day	15mg/day	15mg/ day, can be increased as per info below(*).
Switching from 150mg trazodone to mirtazapine (minimum daily dose)	Trazodone	150mg/day	100mg/day	50mg/day	Stop	Stop
	Mirtazapine	0mg/day	0mg/day	15mg/day	15mg/day	15mg/ day, can be increased as per info below(*).
Switching from 50mg	Trazodone	50mg/day	Stop	Stop	Stop	Stop

trazodone to mirtazapine (minimum daily dose)	Mirtazapine	0mg/day	15mg/day	15mg/day	15mg/day	15mg/ day, can be increased as per info below(*).

*If necessary, mirtazapine can be increased in dose at 15mg intervals up to a maximum of 45mg/day. Mirtazapine begins to exert its effect in general after 1-2 weeks of treatment. Treatment with an adequate dose should result in a positive response within 2-4 weeks. With an insufficient response, the dose can be increased gradually up to the maximum dose.

Amending prescribing – liquid formulation

Trazodone liquid is extremely expensive by comparison with the equivalent dose in capsule form; a 50mg capsule costs £0.27, whereas the same dose in liquid form costs £4.55. For this reason, the unnecessary use of liquid should be challenged and the medication switched to capsules wherever feasible. This is an area that can be actively challenged by primary care teams. If a patient were prescribed 50mg liquid per day when they could instead use capsules, this is an expenditure of £1661 vs. £98 per year.

Liquid should only be prescribed in cases where:

- The patient is unable to swallow capsules
- The dose cannot be achieved using capsules

In other cases the patient should be assessed, and the medication changed to capsule form.

During the audit phase, large cohorts of patients were identified that were being prescribed trazodone liquid split across multiple administrations a day (for example, 25mg BD). This forces practitioners to prescribe the liquid in order to achieve the dose. **In such a case, the dose should be consolidated and a 50mg capsule given at night.**

The half-life of trazodone is 5-13 hours, with an approximate two-fold increase in half life in those aged over 65. This relatively long half-life suggests splitting the dose will have little effect on the therapeutic levels of the medication. The patient will benefit from a reduced "tablet burden", having a single dose of 50mg at night, while the cost burden to providers will also be reduced.

In some cases the second dose of a split medication is given only when the patient has been assessed for drowsiness (a side effect of the medication). If there is a record of such a practice, do not amend the prescription. Discuss with the lead practitioner for that patient dropping the second dose. Furthermore if a patient is regularly suffering such side effects, continued trazodone use should be assessed, and the patient should take the medication at night to lessen the risk of falls.

Withdrawal Effects

Following therapy with Trazodone, particularly for a prolonged period, an incremental dosage reduction to withdrawal is recommended to minimise the occurrence of withdrawal symptoms.

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. Remember by discontinuing/cross-tapering slowly and by educating the patient on what to expect during a switch, the symptoms (and a patient's perception of their severity) will be lessened or avoided entirely.

Advice for patients

A good booklet on "Managing Insomnia and Sleep Problems" is available here.

The booklet includes "10 Rules for Improved Sleep Hygiene";

1	Products containing caffeine (tea, coffee, cocoa, chocolate, soft drinks, etc.) should be discontinued at least 4 hours before bedtime. Caffeine is a stimulant and can keep you awake.
2	Avoid nicotine (including nicotine patches or chewing gum, etc) an hour before bedtime and when waking at night. Nicotine is also a stimulant.
3	Avoid alcohol around bedtime because although it can promote sleep at first, it can disrupt sleep later in the night.
4	Avoid eating a large meal immediately before bedtime, although a light snack may be beneficial.
5	Try to do regular (even mild) physical exercise if you are able, but avoid doing this in the 2 hours before bedtime.
6	Keep the bedroom calm and tidy. Select a mattress, sheets, and pillows that are comfortable.
7	Avoid extreme room temperature in the bedroom.
8	Keep the bedroom quiet and darkened during the night, but try to spend some time in daylight (or bright artificial light) during the day.
9	Keep your bedroom mainly for sleeping; try to avoid watching television, listening to the radio, or eating in your bedroom.
10	Try to keep regular times of going to bed and getting up.

Useful information for older patients can also be found here – (https://mindedforfamilies.org.uk/older-people). This is a free learning resource about mental health. The section on insomnia is useful in describing what normal sleep looks like, and how this changes as people age.

Cost comparisons

Medication	Minimum effective dose	Cost per pack	Cost per year
Trazodone	50mg	£7.54 (28)	£98.02
Sertraline	50mg	£0.80 (28)	£10.40
Mirtazapine	15mg	£1.15 (30)	£13.80

Table 1 - Trazodone prescribing across Nottinghamshire Apr17-Dec 17

	Cost	Rx figs	Average cost per Rx
Mansfield and Ashfield CCG	£ 115,659.83	3636	£ 31.81
Newark and Sherwood CCG	£ 50,730.93	2280	£ 22.25
Notts City CCG	£ 242,112.18	8895	£ 27.22
Notts N&E CCG	£ 103,673.12	3680	£ 28.17
Notts West CCG	£ 85,503.78	3071	£ 27.84
Rushcliffe CCG	£ 71,996.48	2096	£ 34.35
Total	**£ 669,676.32**	23658	£ 28.31

After auditing a practice in Nottingham West CCG, of 81 patients, 29 were be eligible for stopping for swapping the medication as per this document – equating to 36% of the population.

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