Tricyclic Antidepressants (Amitriptyline or Nortriptyline) – Palliative Care (Adults)

Contents

1. Overview

Purpose

This protocol outlines the administration, prescribing and monitoring of the tricyclic antidepressants, amitriptyline and nortriptyline, at Te Whatu Ora - Waitematā.

Scope

All medical and nursing staff.

⚠ This guideline is for use in context of Palliative Care ONLY.

2. Presentation

Amitriptyline 10mg, 25mg and 50mg tablets
Nortriptyline 10mg and 25mg tablets

3. Indications

Licensed:

- Depression, anxiety and panic disorders[1]
- Smoking cessation for nortriptyline.[2]

Unlicensed:

- Neuropathic pain[1, 2]
- Bladder spasms, sweating, drooling and sialorrhoea for amitriptyline.[3]

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4. Mechanism of Action

Tricyclic antidepressants block the pre-synaptic re-uptake of serotonin and noradrenaline. They may also act as a NMDA-receptor antagonist and has a sedative effect which helps to improve sleep.[1, 2] The half-life of amitriptyline ranges from 9 to 25 hours and around 63% is excreted by the kidneys. It is metabolised mainly by the CYP2D6 enzyme to active metabolites.[3]

Nortriptyline is an active metabolite of amitriptyline and is less sedating and has less anticholinergic effects than amitriptyline. It is metabolised mainly by the CYP2D6 enzyme to active metabolites.[2, 3]

5. Dose

NOTE: The use of tricyclic antidepressants in neuropathic pain has reduced significantly due to the increased use/familiarity with gabapentin and pregabalin.

If a tricyclic antidepressant is considered for neuropathic pain or other indication (depression, anxiety or panic disorder), consider using nortriptyline first line which is just as effective as amitriptyline. The anticholinergic effects of nortriptyline are less potent. It is also less sedating than amitriptyline so may be better tolerated.[4]

Indication	Amitriptyline Dose	Nortriptyline Dose
†Neuropathic Pain[3]	• 10 to 150mg oral nocte • Start with 10mg oral nocte and increase according to response and sensitivity (will take 3-7 days to take effect) • If necessary and the patient can tolerate it, after 3-7 days increase to 25mg oral nocte, then after 1-2 weeks increase to 50mg oral nocte • If up-titration is well tolerated and brings *additional benefit*, increase up to a maximum of 150mg oral nocte (rarely required)[2]	• 10 to 50mg oral nocte • Start with 10mg nocte and increase slowly according to response • As this will take 3 to 5 days to take effect, the dose can be increased by 10mg every 3 days as necessary if the patient tolerates it[3, 5]
Depression, anxiety or panic disorders[1, 3]	• Amitriptyline is no longer first-line for depression, anxiety/panic disorders but may have a place for those refractory to other treatments or with co-existing neuropathic pain[2] • 50 to 150mg oral nocte[1, 2] • Start with 10mg oral nocte and increase slowly (doses of up to 200mg may be used although 75-100mg oral nocte is generally as effective as higher doses and better tolerated)[2] • Will take 3-4 weeks to take effect[1]	• 25 to 100mg oral nocte (max of 50mg daily in the elderly)[2] • Start with 25mg nocte (10mg in the elderly) and increase every 2 to 4 weeks according to response[3, 5]

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Drooling and sialorrhoea[3]	• Dose as per neuropathic pain • The benefit is from the antimuscarinic action of amitriptyline (i.e. dry mouth) so switching to nortriptyline in this setting is unhelpful	• Not recommended for this indication

⚠ Lower maintenance doses may be sufficient in renal/hepatic impairment as accumulation may occur.

Note: Avoid stopping tricyclic antidepressants abruptly as it may result in withdrawal symptoms including nausea, headache and malaise. Gradual dose reduction over 1 to 2 weeks is recommended.

6. Administration

- Both only available as oral tablets
- Peak plasma levels can be 2 – 12 hours after oral administration so doses should be given in early evening (up to 2 hours before bedtime) to reduce excessive morning sedation.[1,2,3]

7. Observation and Monitoring

- Monitor for all anti-muscarinic effects (e.g. constipation, dry mouth, urinary retention), increased confusion, excessive sedation and falls.
- Consider blood pressure monitoring when starting tricyclic antidepressants if patient is at risk of postural hypotension (e.g. elderly patients, patients taking cardiac/blood pressure lowering medications).

8. Contraindications and Precautions

Contraindications[1, 2]

- Hypersensitivity to amitriptyline or nortriptyline
- Acute recovery phase following a myocardial infarction[1]
- Concurrent use with monoamine oxidase inhibitor (MAOI) or use of MAOI within two weeks of starting tricyclic antidepressants.

Precautions[1, 2]

- Elderly
- Cardiac disease
- QT prolongation
- Arrhythmias
- History of seizures
- History of mania/Bipolar disorder
- History of urinary retention
- Delirium
- Hyponatraemia
- Hepatic or renal impairment
- Narrow angle glaucoma
- Hyperthryoid patients
- Emergence of suicidal ideation
- Clinical worsening of depression
- Diabetes (increased risk of hypoglycaemia)

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Note: The potential for tricyclics to cause delirium is high (due to their anticholinergic activity) and great care should be exercised when using these agents in the frail elderly, agitated patients or in patients on multiple other medications.

9. Adverse Effects

- Dry mouth
- Blurred vision
- Mydriasis
- Increased intraocular pressure
- Constipation
- Paralytic ileus
- Urinary retention
- Arrhythmias
- Tachycardia
- Palpitations
- Non-specific ECG changes
- Parasthesia
- Postural hypotension
- Hyponatraemia
- Changes in blood sugar control
- Anorexia/Nausea
- Restlessness
- Sedation
- Insomnia/nightmares
- Confusion/delirium
- Hallucinations
- Increased appetite
- Withdrawal on abrupt cessation[1, 2]

10. Drug Interactions

- **AVOID** combination with monoamine oxidase inhibitors (moclobemide) – serotonin syndrome and risk of hypertensive crisis
- Additive risk of serotonin syndrome with selective serotonin reuptake inhibitors (SSRIs) – especially fluoxetine and paroxetine (strong CYP2D6 inhibitors) can increase plasma concentration of amitriptyline by up to 10 times[2]
- Increased effects/side effects of tricyclic antidepressants with CYP2D6 enzyme inhibitors (e.g. fluconazole, terbinafine, cimetidine)
- Other anticholinergic medications (e.g. oxybutynin, orphenadrine, scopolamine, solifenacin)
- Sympathomimetic medications (e.g. noradrenaline, adrenaline)
- Carbamazepine decreases the plasma concentration of tricyclic antidepressants
- Central nervous system depressants (e.g. opiates, alcohol, barbiturates)
- Medications that prolong the QTc interval (e.g. antipsychotics, ondansetron, domperidone, sotalol)
- Concomitant administration of medications known to lower seizure threshold (e.g. tramadol , quinolones)
- Cimetidine and terbinafine increase the plasma concentration of nortriptyline
- Other antidepressants (e.g. venlafaxine).[1, 2, 3, 5]

⚠ **AVOID** combination of monoamine oxidase inhibitor and tricyclic antidepressants.
It is usually avoided and a two week washout period is required.[1, 2]

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11.References

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