Tricyclic Antidepressants

Prescribing Points

Recently we have discussed the place of TCAs in the treatment of depression in the elderly. In the treatment of depression, SSRIs are more commonly used, than TCAs as first-line agents in most situations. TCAs may also cause problematic adverse effects especially in the elderly. In this article we point out that TCAs are still valuable in the management of depression and neuropathic pain.

TCAs are effective antidepressants

Tricyclic antidepressants (TCAs) are as effective as selective serotonin reuptake inhibitors (SSRIs) in the treatment of depression and provide an alternative treatment if an SSRI is unsuitable or not tolerated. In general TCAs are less well tolerated than SSRIs, mainly due to anticholinergic effects, and are more toxic in overdose. In some patients low doses of TCAs (75 – 100 mg daily) may be effective with less adverse effects than higher doses (bpac^{nz}, 2004).

Adverse effects less likely with nortriptyline

TCAs vary in their pharmacological properties and this translates mainly to significant differences in the relative intensity of some adverse effects (Table 1). Amitriptyline and nortriptyline are the most commonly prescribed TCAs in New Zealand, and in general nortriptyline is the preferred agent, as it is less likely to cause troublesome adverse effects. Although amitriptyline may be preferred if sedative effects are specifically required, nortriptyline will often give the desired hypnotic effect with less risk of undesirable effects, if given at night time.

TCAs usually first-line agents in the treatment of neuropathic pain

TCAs are effective agents for the treatment of various types of neuropathic pain and are usually considered first-line agents. Amitriptyline and nortriptyline are equally effective (NNT approximately 3). The best evidence for the effectiveness of TCAs in neuropathic pain is in painful diabetic neuropathy and trigeminal neuralgia. SSRIs (NNT 6.7) and venlafaxine (NNT 4.1 – 5.5) do not appear to be as effective as TCAs (Gilron, 2006). The starting dose of TCA is 10 – 25 mg at night or in divided doses every 12 hours. The daily dose can be increased by 10 – 25 mg every week. The usual effective dose is 50 – 150 mg daily (median 50 – 75 mg daily) (Gilron, 2006).

Table 1: Comparison of Adverse Effects of TCAs

	Anticholinergic	Orthostatic Hypotension	Sedation	Weight Gain	Cardiac Arrhythmias
Amitriptyline	+ + + +	+ + + +	+ + + +	+ + +	+ + +
Nortriptyline	+ +	+	+ +	+	+ +
Doxepin	+ + +	+ +	+ + + +	+ + + +	+ +
Impiramine	+ + +	+ + + +	+ + +	+ + + +	+ + +
***Clomipramine**	+ + + +	+ +	+ + + +	+ + + +	+ + +
****Desipramine**	+	+ +	+ +	+	+ + +
Trimipramine	+ + + +	+ + +	+ + + +	+ + + +	+ + +

From; Drug Information Handbook, 11th Ed. 2003. American Pharmaceutical Association

*Clomipramine has significant serotonergic properties and is usually reserved for specific indications such as Obsessive Compulsive Disorder. Retail Pharmacy Specialist.

** Restricted to Hospital Pharmacy Specialist

Caution with drug interactions

TCAs have numerous clinically significant drug interactions. Some of these involve additive effects when co-prescribed with sedatives, hypnotics and drugs with hypotensive and anticholinergic properties. The metabolising enzyme CYP2D6 is involved in the metabolism of most TCAs and drugs which inhibit this enzyme (e.g. SSRIs, amiodarone, cimetidine, methadone) will increase plasma concentrations of TCAs and dose related adverse effects. TCAs with strong serotonergic properties such as clomipramine have the potential to cause serotonin syndrome with other serotonergic drugs such as tramadol and TCAs. Although controversial, TCAs are sometimes co-prescribed with an SSRI under specialist advice, especially if the patient is having difficulty sleeping. It should be noted that the combination is potentially hazardous due to the increased risk of serotonin syndrome and up to four fold increases in plasma concentrations of the TCA. The smallest possible dose of TCA should be used, usually 10 mg.

Stopping TCAs suddenly can cause withdrawal reactions

If TCAs are stopped suddenly without tapering, patients can experience a withdrawal syndrome characterised by some or all of the following: gastrointestinal disturbances, malaise, chills, anxiety, agitation, sleep disturbances, parkinsonism and mania or hypomania (Dilsaver, 1994).

Most of these symptoms are associated with cholinergic rebound and can be managed by gradual tapering over at least four weeks, or as long as six months in patients who have been receiving long term maintenance therapy.

TCA withdrawal has resulted in cardiac arrhythmias in some patients and seems to be more severe and more common in children.

References

bpac[nz]. Depression POEM 2004. Available from www.bpac.org.nz.

Dilsaver SC. Withdrawal phenomena associated with antidepressant and antipsychotic agents. Drug Safety 1994;10:103-14.

Gilron I, Watson PN, Cahill CM, Moulin D. Neuropathic pain; a practical guide for the clinician. CMAJ 2006;175(3):265-75.