Which TCAs and what dosing is recommended for the different types of chronic non-cancer pain as recommended in the chart for key message 1?

Tricyclic antidepressants (TCAs) are agents approved for the treatment of depression. Their pharmacologic activity involves the antagonism of serotonin and norepinephrine transporters.[1] They may be further classified as secondary or tertiary amines, based on their chemical structure.[2] These agents differ in selectivity for norepinephrine and serotonin, with tertiary amine TCAs showing selectivity for serotonin transporters (i.e., more potent inhibition of serotonin reuptake) and secondary amine TCAs for norepinephrine transporters (i.e., more potent inhibition of norepinephrine reuptake). All of the TCAs competitively antagonize the muscarinic acetylcholine receptors, to varying degrees.[3] For example, anticholinergic effects are more commonly observed with tertiary amine TCAs.[2] TCAs also antagonize peripheral α1-adrenergic receptors and inhibit peripheral and central post-synaptic histamine receptors.[3] These latter mechanisms are largely responsible for toxicities observed with therapeutic dosing and overdosage.

Due to the role of serotonin and norepinephrine in pain transmission, TCAs are commonly used to treat several types of pain.[1] Several organizations suggest that TCAs are effective in the treatment of neuropathic pain and pain accompanied by insomnia, depression, or anxiety.[4-11] Recommendations on TCA use from selected chronic pain guidelines are summarized in Table 1.

Table 1. Recommendations on use of TCAs from selected **chronic pain** guidelines.[4-11]

Organization, year of publication	TCA-related recommendations
ACOEM 2014	• Norepinephrine adrenergic reuptake blocking antidepressants are listed as examples of first-line medications for pain therapy. • **Does not specify which TCA(s) to use.**
ASA/ASRA 2010	• TCAs should be used as part of a multimodal approach for a variety of patients with chronic pain. • **Does not specify which TCA(s) to use**, but lists the following as examples: amitriptyline, nortriptyline, desipramine, imipramine.
ASIPP 2012	• In patients with neuropathic pain resistant to opioids, TCAs in combination with higher opioid doses may be needed. • **Does not specify which TCA(s) to use.**
CDC 2016	• TCAs are effective for neuropathic pain conditions including diabetic neuropathy and post-herpetic neuralgia, usually at lower doses than those recommended for treatment of depression. TCAs can also be used to treat fibromyalgia. • **Does not specify which TCA(s) to use.**
Colorado Department of Labor and Employment 2012	• TCAs are first-line agents for neuropathic pain. • **Newer formulations (e.g., nortriptyline and desipramine) have better side effect profiles compared to older formulations (e.g., amitriptyline and imipramine).** • Dosing varies by agent, but low dosages (e.g., <100 mg/day) are recommended for chronic pain and/or insomnia. Lower doses also reduce the risk of adverse effects.
ICSI 2013	• TCAs are recommended for treatment of neuropathic pain, especially in patients with co-existing insomnia, anxiety, or depression. • **Tertiary and secondary amines are effective, but tertiary amines are associated with more anticholinergic side effects and should be avoided in elderly patients. Nortriptyline and desipramine are listed as examples of secondary amines; amitriptyline and imipramine are listed as examples of tertiary amines.** • Analgesia may be seen at lower doses than those recommended for treatment of depression; TCAs should be initiated at low doses; doses should be gradually increased over several weeks to months.

Organization, year of publication	TCA-related recommendations
VA/DoD 2010	• Antidepressants should be considered as adjuvant therapy to manage irritability and sleep disturbances • **Does not specify which TCA(s) to use.**
Washington State Interagency 2015	• TCAs should be considered for neuropathic pain, other centralized pain syndromes, or fibromyalgia. TCAs may also facilitate sleep initiation and maintenance. • **Nortriptyline and desipramine are listed as options for treating chemotherapy-induced peripheral neuropathy and chronic post-operative neuropathic pain syndromes.** • **TCAs to use for other types of neuropathic pain conditions are not specified.** • Low doses of TCAs are recommended. Doses are not specified. • Patients on TCAs should be monitored for cognitive impairment or sedation.

ACOEM=American College of Occupational and Environmental Medicine; ASA=American Society of Anesthesiologists; ASIPP=American Society of Interventional Pain Physicians; ASRA=American Society of Regional Anesthesia; CDC=Centers for Disease Control and Prevention; ICSI=Institute for Clinical Systems Improvement; VA/DoD=Veterans Affairs/Department of Defense

Several organizations recommend TCAs for neuropathic pain; however, as noted in Table 1, many do not specify which TCAs to use, nor do they recommend specific dosages.[4-11] The Colorado Department of Labor and Employment[7] and Institute for Clinical Systems Improvement (ICSI)[9] do state that secondary amine TCAs are preferred to tertiary amine TCAs due to their safety profile.

In addition to these pain guidelines, guidelines specific to the management of neuropathic pain were reviewed.[12-17] Recommendations on TCA use identified in these guidelines are outlined in Table 2.

Table 2. Recommendations on use of TCAs from selected **neuropathic pain** guidelines.[13-17]

Organization, year of publication	TCA-related recommendations[a]
AAN 2011	• **Amitriptyline should be considered for treatment of painful diabetic neuropathy.** • There is insufficient evidence to support or refute the use of desipramine, imipramine, or the combination of nortriptyline and fluphenazine in the treatment of painful diabetic neuropathy.
Canadian Pain Society 2014	• TCAs are first-line agents for chronic neuropathic pain. If patients fail TCA monotherapy, combination or mono-therapy with a gabapentinoid or SNRI (e.g., duloxetine) may be considered. Of note, gabapentinoids and SNRIs are recommended as first-line agents, as well. • **Secondary amines (nortriptyline and desipramine) are better tolerated than tertiary amines (amitriptyline and imipramine) with comparable analgesic efficacy.** • Recommended starting doses (listed for amitriptyline, nortriptyline, and desipramine) are 10-25 mg/day; doses may be increased weekly by 10 mg/day with usual maintenance doses of 10-100 mg/day.
EFNS 2010	• TCAs are first-line agents for diabetic neuropathy, post-herpetic neuralgia, and central neuropathic pain (specifically, spinal cord injury and central post-stroke pain). • TCAs include amitriptyline, clomipramine, nortriptyline, desipramine, and imipramine. **Amitriptyline is recommended for central pain, and clomipramine is recommended only for diabetic neuropathy. TCAs to use for different types of neuropathic pain are not otherwise specified.** • Recommended doses range from 25 to 150 mg/day. Doses for individual agents are not specified.

Organization, year of publication	TCA-related recommendations[a]
NeuPSIG 2007	• TCAs are efficacious in the treatment of neuropathic pain, particularly post-herpetic neuralgia and painful diabetic peripheral neuropathy. • **Secondary amine TCAs (nortriptyline, desipramine) recommended as first-line options for treatment of neuropathic pain. Tertiary amine TCAs are recommended only if a secondary amine TCA is not available,** because secondary amines are better tolerated. Tertiary and secondary amine TCAs are comparable in analgesic efficacy. • The recommended starting dose of secondary amine TCAs is 25 mg at bedtime. Doses may be titrated every 3-7 days as tolerated by 25 mg/day. The maximum recommended dose is 150 mg/day. An adequate trial duration is 6-8 weeks with at least 2 weeks at maximum tolerated dose. • In general, starting doses of TCAs should be low, and doses should be titrated slowly until pain is adequately controlled or tolerability limits further increases.
NICE 2013	• NICE recognizes TCAs as examples of commonly used pharmacological treatments for neuropathic pain. • From a review of randomized controlled trials, among the TCAs, **amitriptyline consistently showed pain reduction vs. placebo;** the majority of data reviewed also indicated pain reduction with nortriptyline vs. placebo. Results for imipramine and nortriptyline in combination with gabapentin (i.e., nortriptyline + gabapentin) vs. placebo were inconclusive. • The GDG noted that side effects of amitriptyline, e.g., sedation, may be intolerable by some patients but may be considered beneficial by patients with sleep problems. • The GDG also noted that nortriptyline may be better tolerated than amitriptyline but found that estimates of nortriptyline's effectiveness were highly uncertain, prompting them to not make explicit recommendations regarding nortriptyline.

AAN=American Academy of Neurology; EFNS=European Federation of Neurological Societies; GDG=Guideline Development Group; NeuPSIG=Neuropathic Pain Special Interest Group (of the International Association for the Study of Pain); NICE=National Institute for Health and Care Excellence; SNRI=serotonin-norepinephrine reuptake inhibitor
[a]TCAs are listed among several first-line options for neuropathic pain.

Unlike the majority of chronic pain guidelines reviewed (see Table 1), several of the neuropathic pain guidelines include specific recommendations regarding usage of individual TCAs.[4-11,13-17] Notably, there are some differences in recommendations. Like the Colorado Department of Labor and Employment and ICSI,[8,9] the Canadian Pain Society[14] and the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain[16] recommend secondary amine TCAs over tertiary amine TCAs. In contrast, the National Institute for Health and Care Excellence (NICE) states that the effectiveness of nortriptyline is uncertain, thus precluding any recommendations on its use.[17] Instead, NICE recommends amitriptyline as a TCA with consistent evidence of pain reduction compared to placebo. The American Academy of Neurology (AAN)[13] and the European Federation of Neurological Societies (EFNS)[15] also recommend amitriptyline, for painful diabetic neuropathy and central neuropathic pain, respectively.

A search of the literature was performed to identify studies involving the use of TCAs for neuropathic pain. A meta-analysis and several Cochrane reviews were identified.[18-21] Finnerup et al conducted a meta-analysis of randomized, double-blind controlled trials evaluating oral and topical pharmacotherapy for neuropathic pain.[18] Their intent was to use these results to revise/update the NeuPSIG recommendations for treatment of neuropathic pain. TCAs were included in the meta-analysis, as well as several other drugs (e.g., serotonin-norepinephrine reuptake inhibitors [SNRIs], pregabalin, gabapentin, tramadol, opioids, cannabinoids, lidocaine, capsaicin). The investigators only included studies involving at least 10 patients per group and a minimum treatment duration of 3 weeks. The primary measure of effect was number needed to treat (NNT) for 50% reduction in pain intensity, or ≥30% pain reduction or moderate pain relief. The investigators also reviewed tolerability and safety, and drug costs. A total of 229 studies were included in their analyses; TCAs were involved in 15 comparisons with placebo. Amitriptyline was assessed in 12 trials, at doses of 25-150 mg/day. Other TCAs assessed were doxepin, clomipramine, imipramine, desipramine, and nortriptyline. The overall number of patients experiencing pain relief on TCAs was 217/473 (45.9%) vs. 85/475 on placebo (17.9%), and the calculated NNT

was 3.6 (95% confidence interval [CI] 3.0 to 4.4). This NNT was considered "low" by the investigators. For indirect comparison, the NNT was 6.4 (95% CI 5.2 to 8.4) for SNRIs, 7.7 (95% CI 6.5 to 9.4) for pregabalin, 7.2 (95% CI 5.9 to 9.1) for gabapentin, and 4.7 (95% CI 3.6 to 6.7) for tramadol. Of note, the efficacy was found to be similar across the TCAs. Overall, the quality of evidence for TCAs was deemed moderate.

Based on their findings, Finnerup et al concluded that TCAs (as well as SNRIs, pregabalin, and gabapentin) should be used as first-line agents for neuropathic pain.[18] They also advised that TCAs should be administered at doses of 25-150 mg, once daily or in 2 divided doses, except for tertiary amines (e.g., amitriptyline, imipramine, clomipramine), which should be administered at doses of <75 mg/day in adults aged >65 years, based on 2012 Beers Criteria.

In addition to this meta-analysis, Cochrane reviews of 3 of the TCAs (imipramine, desipramine, and amitriptyline) were identified.[19-21] Hearn et al assessed the efficacy of imipramine for chronic neuropathic pain based on double-blind, randomized controlled trials in which patients received treatment for ≥2 weeks.[19] The investigators defined primary outcomes as proportion of patients with ≥50% or 30% reduction in pain or equivalent and Patient Global Impression of Change (PGIC) scores. The investigators identified 5 studies involving 168 patients with painful diabetic neuropathy or polyneuropathy. Patients received imipramine at doses of 25-350 mg/day (most commonly 100-150 mg/day). Comparators included placebo, paroxetine, mianserin (drug not approved in the United States), venlafaxine, and amitriptyline. Treatment duration ranged from 2 to 12 weeks. The investigators stated that there were significant limitations in all of these trials; each study had ≥1 source of potential major bias (e.g., small sample size), and none of the studies evaluated proportion of patients with ≥50% or 30% pain reduction. Only 1 study evaluated PGIC. The investigators stated that pooling the data was not possible. Among the individual studies, the placebo-controlled data suggested increased pain relief with imipramine, but Hearn et al stated that these data were of low quality, as they were derived from group mean data and completer analyses, in small studies of short duration. Hearn et al concluded that there was little evidence to support the use of imipramine for chronic neuropathic pain.

Hearn et al also investigated the efficacy of desipramine for neuropathic pain,[20] using the same methodology as in their review of imipramine.[19] They identified 5 studies involving 177 patients with painful diabetic neuropathy or postherpetic neuralgia.[20] Of these, 145 patients were randomized to receive desipramine 12.5-250 mg/day, with most taking 100-150 mg/day. Comparators included placebo, fluoxetine, clomipramine, and amitriptyline, and treatment duration ranged from 2 to 6 weeks. Like the studies identified in their review of imipramine, all of these studies had ≥1 source of potential major bias, and none of the studies reported the proportion of patients with ≥50% or 30% pain reduction. Pooling of data was also not possible. Individual trial data suggested some improvement in pain relief with desipramine compared to placebo, but Hearn et al asserted that these data were of low quality. The number of participants in active-controlled studies was also deemed to be too low to draw conclusions about the comparative efficacy of desipramine. Thus, Hearn et al concluded that there was little evidence to support the use of desipramine for chronic neuropathic pain.

Most recently, Moore et al evaluated the efficacy of amitriptyline for chronic neuropathic pain, reviewing double-blind, randomized controlled trials in which patients received treatment for ≥4 weeks.[21] In total, they identified 17 trials with 1342 patients for inclusion in their analyses. They commented that most of these studies were at high risk of bias due to small sample size. Only 7 of the studies were thought to report useful efficacy data. For only 2 of these studies, amitriptyline was associated with significantly greater improvement in pain relief compared to placebo. Based on their findings, Moore et al concluded that there is no supportive unbiased evidence for amitriptyline use in neuropathic pain; however, they stated that this should be considered along with decades of treatment success in clinical practice, and that these data do not suggest lack of effect but rather a possible overestimation of treatment effect. Moore et al further recommended that clinicians continue to use amitriptyline as part of the treatment for neuropathic pain, with the understanding that only a minority of patients may achieve satisfactory pain relief.

A list of TCAs available in the United States is presented in Table 3, along with dosage and administration recommendations derived from the drug labels and previously reviewed guidelines.[3,14-16,22-33] Importantly, the safety and tolerability of TCAs should be considered before initiating therapy. TCAs historically were the dominant class of antidepressants until the development of selective serotonin reuptake inhibitors (SSRIs); their use has fallen out of favor primarily due to their side effects.[1] Antagonism of muscarinic acetylcholine receptors leads to impaired cognition as well

as several adverse effects on the parasympathetic nervous system (e.g., blurred vision, dry mouth, tachycardia, constipation, and difficulty urinating). TCAs may also cause orthostatic hypotension, due to antagonism of α1-adrenergic receptors, and sedation, due to antagonism of α1-adrenergic and histamine receptors. Other adverse effects reported with TCAs include weight gain, cardiac arrhythmias, and seizures. Some differences among the TCAs have been reported in the risk of certain adverse effects – see Table 4.[1,22] Though distinctions have been made between secondary and tertiary amine TCAs, the American Geriatrics Society strongly recommends avoiding all TCAs in elderly patients due to the risk of sedation, orthostatic hypotension, and other anticholinergic effects in their 2015 update of the Beers Criteria.[34] Also of note, all TCAs have boxed warnings for an increased risk of suicidal thinking and behavior in pediatric patients and young adults with major depressive disorder and other psychiatric disorders.[24-33]

Table 3. Selected characteristics of TCAs. [3,14-16,22-33]

Drug name (brand)	Available oral dosage forms	FDA-approved uses	Dosage and administration		Notes[a]
			Depression[a]	Neuropathic pain[b,c]	
Secondary amines					
Amoxapine (Asendin®)[d]	25, 50, 100, 150 mg tablets	Relief of symptoms of depression accompanied by anxiety or agitation	Initial: 50 mg, 2 or 3 times daily Usual maintenance: 200-300 mg daily Maximum: 400 mg daily; 300 mg daily in elderly patients	Initial: 25 mg at bedtime Maximum: 150 mg daily	Doses >300 mg should be given in divided doses.
Desipramine (Norpramin®)	10, 25, 50, 75, 100, 150 mg tablets	Treatment of depression	Initial: "low level"; dose not specified Usual maintenance: 100-200 mg daily Maximum: 300 mg daily	Initial: 10-25 mg daily Usual maintenance: 10-100 mg daily Maximum: 150 mg daily	When initiated, may be administered in divided doses or once daily.
Nortriptyline (Pamelor®)	10, 25, 50, 75 mg capsules 10 mg/5 mL solution	Relief of symptoms of depression	Initial: "low level"; dose not specified Usual maintenance: 25 mg, 3 or 4 times daily; 30-50 mg daily in adolescent and geriatric patients Maximum: 150 mg/day	Initial: 10-25 mg daily Usual maintenance: 10-100 mg daily Maximum: 150 mg daily	Doses may be administered once daily.
Protriptyline (Vivactil®)[d]	5, 10 mg tablets	Treatment of depression	Initial: "low level"; dose not specified Usual maintenance: 15-40 mg/day, divided into 3 or 4 doses; 5 mg, 3 times daily in adolescent and geriatric patients Maximum: 60 mg/day	Initial: 25 mg at bedtime Maximum: 150 mg daily	Close monitoring recommended in elderly patients taking >20 mg/day.
Tertiary amines					
Amitriptyline (Elavil®, others)	10, 25, 50, 75, 100, 150 mg tablets	Relief of symptoms of depression	Initial and usual maintenance: 50-100 mg at bedtime; 10 mg 3 times daily + 20 mg at bedtime in adolescent and geriatric patients Maximum: 150 mg daily (outpatient); 300 mg daily (inpatient)	Initial: 10-25 mg daily Usual maintenance: 10-100 mg daily Maximum: 150 mg daily	None.

Drug name	Available oral	FDA-approved uses	Dosage and administration		Notes[a]
Clomipramine (Anafranil®)	25, 50, 75 mg capsules	Treatment of obsessive-compulsive disorder	Initial: 25 mg daily; titrate to 100 mg daily in first 2 weeks Maximum: 250 mg daily at bedtime	Initial: 25 mg at bedtime Maximum: 150 mg daily	Doses may be divided and administered with meals to reduce gastrointestinal side effects.
Doxepin (Adapin®[d], Sinequan®[d], Silenor®)	10, 25, 50, 75, 100, 150 mg capsules 3, 6 mg capsules (Silenor®)	Treatment of depression and/or anxiety, associated with alcoholism or organic disease, and psychotic depressive disorders with associated anxiety Treatment of insomnia characterized by difficulty with sleep maintenance (Silenor®)	Initial: 75 mg /day Usual maintenance: 75-150 mg/day; 300 mg/day may be required in severely ill patients	Initial: 25 mg at bedtime Maximum: 150 mg daily	Doses may be divided or administered once daily.
Imipramine (Tofranil®, others)	10, 25, 50 mg tablets 75, 100, 125, 150 mg capsules (imipramine pamoate)	Relief of symptoms of depression Adjunctive therapy for childhood enuresis	Initial: 75 mg/day, increased to 150 mg/day (outpatient); 100 mg/day, in divided doses, increased to 200 mg/day (inpatient); 30-40 mg/day in adolescent and geriatric patients, increased to ≤100 mg/day Usual maintenance: 50-150 mg/day (outpatient); 250-300 mg/day (inpatient)	Initial: 25 mg at bedtime Maximum: 150 mg daily	None.

Drug name	Available oral	FDA-approved uses	Dosage and administration		Notes[a]
Trimipramine (Surmontil®)	25, 50, 100 mg capsules	Relief of symptoms of depression	Initial: 75 mg/day, increased to 150 mg/day (outpatient); 100 mg/day, in divided doses, increased to 200 mg/day (inpatient); 50 mg/day in adolescent and geriatric patients, increased to 100 mg/day Usual maintenance: 50-150 mg/day (outpatient); 250-300 mg/day (inpatient)	Initial: 25 mg at bedtime Maximum: 150 mg daily	Total dosage may be administered at bedtime.

FDA=Food and Drug Administration
[a]Manufacturer-recommended dosage and administration. Recommendations for indications other than depression not included.
[b]Recommendations based on NeuPSIG 2007, EFNS 2010, and/or Canadian Pain Society 2014 neuropathic pain guidelines.
[c]TCAs should be started at a low dose and titrated up slowly until pain is adequately controlled or tolerability limits further increases. NeuPSIG recommends titrating the dose every 3-7 days as tolerated by 25 mg/day to a maximum of 150 mg/day.
[d]Branded product no longer available

Table 4. Selected side effects of TCAs, reproduced from *Goodman and Gilman's Manual of Pharmacology and Therapeutics*.[1,22]

Drug	Side effect								
	Agitation	Seizure	Sedation	Hypotension	Anti-cholinergic[a]	GI[b]	Weight gain	Sexual[c]	Cardiac[d]
Secondary amines									
Amoxapine	0	2+	+	2+	+	0/+	+	2+	2+
Desipramine	+	+	0/+	+	+	0/+	+	2+	2+
Nortriptyline	0	+	+	+	+	0/+	+	2+	2+
Protriptyline	2+	2+	0/+	+	2+	0/+	+	2+	3+
Tertiary amines									
Amitriptyline	0	2+	3+	3+	3+	0/+	2+	2+	3+
Clomipramine	0	3+	2+	2+	3+	+	2+	3+	3+
Doxepin	0	2+	3+	2+	2+	0/+	2+	2+	3+
Imipramine	0/+	2+	2+	2+	2+	0/+	2+	2+	3+
Trimipramine	0	2+	3+	2+	3+	0/+	2+	2+	3+

GI=gastrointestinal; 0=negligible; 0/+=minimal; +=mild; 2+=moderate; 3+=moderately severe; 4+=severe
[a]Anticholinergic effects include blurred vision, dry mouth, tachycardia, constipation, difficulty urinating
[b]Gastrointestinal effects include abdominal pain, nausea, vomiting, constipation
[c]Sexual effects include breast enlargement and galactorrhea in females, gynecomastia in males, changes in libido, menstrual irregularity
[d]Cardiac effects include arrhythmias, heart failure, myocardial infarction

In summary, TCAs as a class are recommended by several organizations as first-line agents for treatment of neuropathic pain.[4-11,13-17] Few of these organizations specify which TCAs to use; among those with more specific recommendations, secondary amine TCAs such as desipramine and norepinephrine appear to be preferred to tertiary amine TCAs, due to their safety profile.[8,9,14,16] As an exception, amitriptyline is recommended by the AAN and EFNS for painful diabetic neuropathy and central neuropathic pain, respectively, and NICE asserts that data for pain relief with amitriptyline is consistent, unlike the data for other TCAs.[13,15,17] Based on the reviewed literature, there is a paucity of data in the form of randomized controlled trials to support the use of some of the TCAs;[19-21] however, as stated by Cochrane reviewers Moore et al, there is evidence of treatment success in clinical practice that should not be ignored.[21] Importantly, clinicians should also consider the risk of adverse effects with these agents, which may require monitoring before and during therapy.

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