Evidence-to-Decision table 5.3.2		
In adults (including older persons) and adolescents with cancer-related neuropathic pain, what is the evidence for the use of anti-depressants compared to other anti-depressants in order to relieve pain?		

POPULATION:	Adults (including older persons) and adolescents with cancer-related pain	**Background:**
		
		Cancer-related neuropathic pain is common. It can be caused by the disease or due to acute or chronic effects of cancer treatment. Anti-depressants used in neuropathic pain treatment include tricyclic antidepressants (TCAs) and selective serotonin norepinephrine reuptake inhibitors (SNRIs). Evidence exists that might suggest their efficacy in neuropathic pain.[152]
		
		Current WHO recommendation:
		
		• As with nociceptive pain, pharmacotherapy is the mainstay of management for neuropathic pain. One or more of the following groups of medications may help:
		  ○ Tricyclic antidepressants
		  ○ Anticonvulsants
		  ○ Local anaesthetic congeners (class I anti-arrhythmics)
		• Patients with neuropathic pain may derive benefit from opioids, particularly in cases of nerve compression. However, nerve compression pain may respond only if a corticosteroid is added. Mixed nociceptive and neuropathic pain will also benefit from morphine. Superficial burning pain and spontaneous stabbing pain associated with nerve injury often responds best to a tricyclic antidepressant or an anticonvulsant.
		• With regard to tricyclic antidepressants- Amitriptyline and imipramine are both widely available. Alternative preparations are available in many countries and may be more suitable for some patients. Nortriptyline does not have a sedative effect; desipramine is relatively non-sedative and has minimal anticholinergic.
		The starting dose will depend on the patient's age, weight, previous use of such medications and concurrent medication. A dose as low as 10mg may be appropriate for some patients, but most can take 25-50mg. The dose should be increased to 30-50mg as rapidly as can be tolerated in terms of sedation, postural hypotension and dry mouth. After that, increments should be made on a weekly basis until the pain is relieved or adverse

INTERVENTION:	Anti-depressants	
COMPARISON:	Anti-depressants	
MAIN OUTCOMES:	• Pain relief • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Sedation (adverse event) • Anxiety or tremor (adverse event)	
STRATIFICATIONS:	• Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain	
SETTING:	All	
PERSPECTIVE:	Population	

		effects preclude further escalation. Except with nortriptyline, the total daily dose should be given at bedtime, because most tricyclic antidepressants have a sedative effect. An analgesic effect is seen in many patients after a few days on doses of 50-100mg. The pain is always completely relieved.

	CRITERIA	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	**Research evidence** Cancer-related neuropathic pain is common. It can be caused by the disease or due to acute or chronic effects of cancer treatment. Anti-depressants used in neuropathic pain treatment include tricyclic antidepressants (TCAs) and selective serotonin norepinephrine reuptake inhibitors (SNRIs). Some evidence exists to suggests their efficacy in neuropathic pain[152]. WHO should issue updated guidance on their use. **Additional considerations** None

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes ☐ No ☐ Uncertain ☒ Yes	• **No randomized controlled trials** compared anti-depressants to other anti-depressants **BENEFITS and HARMS** • **No trial** reported on **pain relief**. • **No trial** reported on **pain relief speed**. • **No trial** reported on **pain relief maintenance**. • **No trial** reported on **QoL**. • **No trial** reported on **functional outcomes**. • **No trial** reported on **sedation**. • **No trial** reported on **anxiety or tremor**. **STRATIFICATIONS** • Studies conducted in adults with a wide age range, without stratification into adolescent, non-older persons, and older persons. • Studies provide no data regarding history of substance abuse. • Studies provide no data regarading refractory pain. **SUMMARY** No eligible trials were found that address this sub-question.

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability [ ] Minor variability [ ] Uncertain [Yes] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [Yes]	**<u>Research evidence</u>** None **<u>Additional considerations</u>** None

FEASIBILITY ./ RESOURCE USE	**How large are the resource requirements?** Major Minor Uncertai ☐ ☐ Yes **Is the option feasible to implement?** Yes No Uncertain ☐ ☐ Yes	**Research evidence** None **Additional considerations** None
	Would the option improve equity in health? Yes No Uncertai ☐ ☐ Yes	**Research evidence** None **Additional considerations** None

Recommendation	**Current recommendation:** As with nociceptive pain, pharmacotherapy is the mainstay of management for neuropathic pain. One or more of the following groups of medications may help: • Tricyclic antidepressants • Anticonvulsants • Local anaesthetic congeners (class I anti-arrhythmics) Patients with neuropathic pain may derive benefit from opioids, particularly in cases of nerve compression. However, nerve compression pain may respond only if a corticosteroid is added. Mixed nociceptive and neuropathic pain will also benefit from morphine. Superficial burning pain and spontaneous stabbing pain associated with nerve injury often responds best to a tricyclic antidepressant or an anticonvulsant. With regard to tricyclic antidepressants- Amitriptyline and imipramine are both widely available. Alternative preparations are available in many countries and may be more suitable for some patients. Nortriptyline does not have a sedative effect; desipramine is relatively non-sedative and has minimal anticholinergic. The starting dose will depend on the patient's age, weight, previous use of such medications and concurrent medication. A dose as low as 10mg may be appropriate for some patients, but most can take 25-50mg. The dose should be increased to 30-50mg as rapidly as can be tolerated in terms of sedation, postural hypotension and dry mouth. After that, increments should be made on a weekly basis until the pain is relieved or adverse effects preclude further escalation. Except with nortriptyline, the total daily dose should be given at bedtime, because most tricyclic antidepressants have a sedative effect. An analgesic effect is seen in many patients after a few days on doses of 50-100mg. The pain is always completely relieved. In children, the recommended starting dose is 0.5 mg/kg of body weight, increasing to 1 mg/kg if necessary. **New (draft) recommendation:** None

Strength of Recommendation	
Quality of Evidence	➢ None [Omitted for no data]
Justification	The GDG could not make a recommendation for one antidepressant over others due to lack of evidence.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	