Evidence-to-Decision table 5.3.1		
In adults (including older persons) and adolescents with cancer-related neuropathic pain, what is the evidence for the use of anti-depressants compared to placebo 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). Some evidence exists to suggests 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 anesthetic congeners (class I antiarrhythmics) • 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 nonsedative 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
INTERVENTION:	Anti-depressants	
COMPARISON:	Placebo (no treatment)	
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	

		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?** Yes	**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	• **One randomized controlled trial** compared an anti-depressant to placebo. The trial evaluated amitriptyline in people with severe neuropathic cancer pain (cancer types not reported). The trial did not report participant ages. **BENEFITS and HARMS** • **One trial** provided **low strength of evidence** that **anti-depressants (amitriptyline) are more effective than placebo to reduce pain** (difference between groups -4.7 [95% CI -9.2, -0.2] on a transformed 0 to 100 [worst] scale). • **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 **somnolence** as an adverse event. • **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** Anti-depressants probably provide greater pain relief than placebo.

ACCEPTABILITY & PREFERENCES	**Is there important uncertainty or variability about how much people value the options?** Major variability [ ] Minor variability [Yes] Uncertain [ ] **Is the option acceptable to key stakeholders?** Yes No Uncertain [Yes] [ ] [ ]	**<u>Research evidence</u>** None **<u>Additional considerations</u>** The GDG believed that some patients could have strong aversions to the use of antidepressants.

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:** None. **New (draft) recommendation:** None.
Strength of Recommendation	
Quality of Evidence	➢ **LOW** [Pain (critical) = low others omitted for no data]
Justification	While the GDG agreed that antidepressants have been found in decades of clinical practice to be effective in neuropathic pain syndromes, they cannot say that evidence suggests their effectiveness in tumour-related neuropathy. They therefore opted to make no recommendation due to lack of evidence.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	RCTs that assess the intervention in this population of patients, measured by comparable outcomes, are required to justify the indication of anti-depressants for cancer-related neuropathic pain.