Evidence-to-Decision table 5.4.2		
In adults (including older persons) and adolescents with cancer-related neuropathic pain, what is the evidence for the use of second generation anti-epileptics or first generation anti-epileptics such as carbamezapine or sodium valproate compared other anti-epileptics in order to achieve pain control?		
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. Certain antiepileptics are reported to be effective for treatment of neuropathic pain[152], including gabapentin, pregabalin, carbamazepine and valproate. Gabapentin is widely used and was considered for inclusion on WHO EML for neuropathic pain but was not included because of its uncertain benefits. Additional evidence cited in the Technical Report Series for the EML 2017 (but not included in the application) recounted the following history, quoted from [157] in full: *'In 1993, gabapentin (Neurontin®, Pfizer) was first approved by the U.S. Food & Drug Administration (FDA) as an adjunctive therapy for epilepsy. In 2002, the drug was approved for the management of post-herpetic neuralgia, its only pain-related indication.* *Parke-Davis and Pfizer, the companies responsible for promoting and marketing gabapentin, adopted a publication strategy "to disseminate the information as widely as possible through the world's medical literature"[158]. This promotion was judged to be illegal and fraudulent: in 2004, American pharmaceutical manufacturer Warner-Lambert pleaded guilty and agreed to pay more than US$ 430 million to resolve criminal charges and civil liabilities in connection with its Parke-Davis division's marketing scheme of unapproved uses of gabapentin[159]. This was one of the largest settlements reached between the United States Department of Justice and pharmaceutical companies.* *Following litigation, internal company documents relating to gabapentin publication strategy have been made publicly available through two separate legal actions[160,161]. These sources were analysed in a series of studies [162-165] that documented publication and outcome reporting biases and data manipulation. The magnitude of these biases is highly relevant,*
INTERVENTION:	Anti-epileptics	
COMPARISON:	Anti-epileptics	
MAIN OUTCOMES:	• Pain relief • Pain relief speed • Pain relief maintenance • Quality of life (QoL) • Functional outcomes • Sedation (adverse event) • Confusion (adverse event)	
STRATIFICATIONS:	• Age (adults, older persons, adolescents, children) • History of substance abuse • Refractory pain	
SETTING:	All	
PERSPECTIVE:	Population	

		and affects the evidence presented in the application. Firstly, in 2009, of 20 clinical trials for which internal documents were available from Pfizer and Parke-Davis, eight were never published. Secondly, there were irreconcilable differences between the original protocols, statistical analysis plans, interim research reports and the main publications relating to most trials. For eight of the 12 published trials, the primary outcome defined in the published report differed from that described in the protocol. In three out of 10 trials, the numbers of participants randomized and analysed for the primary outcome and the type of analysis for efficacy and safety in the internal research report and the trial publication differed. Different subsets of participants were included in the analysis, leading to different findings: in one trial, the main findings in the publication did not include data from 40% of participants actually randomized. These changes are likely to have unbalanced the comparisons, favouring responsive patients and excluding poor responders in the arms allocated to gabapentin, thereby inflating the size of the effect attributable to the drug. *The important differences between the internal and published documents about the number of patients or the plans of the analyses invalidate the study design (i.e. downgrading the evidence from experimental to observational), as the randomization is no longer valid.'* **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 antiepileptic.

		With regard to anti-epileptics, extensive clinical experience supports the use of anticonvulsants such as carbamazepine and valproic acid in the treatment of nerve injury pain, particularly stabbing pain. The starting dose of carbamazepine is 100mg twice daily. This can be increased slowly, at a rate of 200mg every few days. Carbamazepine causes enzyme auto-induction, thereby enhancing its own metabolism. This is one reason why initial adverse effects (e.g. drowsiness, ataxia) improve with time. Carbamazepine occasionally causes leukopenia. Carbamazepine may exacerbate pre-existing chemotherapy-induced suppression of bone marrow. *[This medication should not be used in children under six years of age. In older children, start by giving 100mg/day (2—3 mg/kg of body weight), and increase in stages to 500mg/day it necessary.]* Valproic acid has a long plasma half-life and is sedative. It may conveniently be given as a single dose at bedtime, at a starting dose of 500 mg, or 200mg for older persons. The dose may be increased by 200mg, if necessary, every 3-4 days to a maximum of 1—1.5g. As the medication accumulates in the body, the dose may subsequently have to be reduced. *[Valproic acid should not be used in children under two years of age because of the danger of hepatotoxicity, which may be fatal.]*

	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. Certain anti-epileptics are reported to be effective for treatment of neuropathic pain[152], although some of the evidence for gabapentin in now disputed (see 'Background' section for this question). **Additional considerations** None

BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Yes: ☐ No: ☐ Uncertain: ☒ Yes	• **One randomized controlled trial** compared anti-epileptics. The **trial compared pregabalin and gabapentin** among patients with cancer-related neuropathic pain. Demographic characteristics such as age were not reported in the trial. **BENEFITS and HARMS** • **One trial** provided **low strength of evidence** that **pain relief was greater in patients taking pregabalin than gabapentin**. The net difference in pain scores (transformed to 0 to 100 [worst] scale) between arms was -8.4 (95% CI -16.5, -0.3). • **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 **confusion**. **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** Pregabalin may improve pain relief.

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 antiepileptic. With regard to anti-epileptics, extensive clinical experience supports the use of anticonvulsants such as carbamazepine and valproic acid in the treatment of nerve injury pain, particularly stabbing pain. The starting dose of carbamazepine is 100mg twice daily. This can be increased slowly, at a rate of 200mg every few days. Carbamazepine causes enzyme auto-induction, thereby enhancing its own metabolism. This is one reason why initial adverse effects (e.g. drowsiness, ataxia) improve with time. Carbamazepine occasionally causes leukopenia. Carbamazepine may exacerbate pre-existing chemotherapy-induced suppression of bone marrow. *[This medication should not be used in children under six years of age. In older children, start by giving 100mg/day (2—3 mg/kg of body weight), and increase in stages to 500mg/day it necessary.]* Valproic acid has a long plasma half-life and is sedative. It may conveniently be given as a single dose at bedtime, at a starting dose of 500 mg, or 200mg for older persons. The dose may be increased by 200mg, if necessary, every 3-4 days to a maximum of 1—1.5g. As the medication accumulates in the body, the dose may subsequently have to be reduced. *[Valproic acid should not be used in children under two years of age because of the danger of hepatotoxicity, which may be fatal.]* **New (draft) recommendation:** None

Strength of Recommendation	
Quality of Evidence	➢ **LOW** [Pain (critical) = low other outcomes omitted for no data]
Justification	The findings of the review were called into doubt in light of fraudulent gabapentin data, discussed in the 'Background' section of this question, which the GDG were alerted to at the guideline formulation meeting. This revelation prevented a recommendation from being made due to lack of evidence.
Subgroup considerations	
Implementation considerations [incl. M&E]	
Research priorities	