Article:
Jordan, RI, Mulvey, MR orcid.org/0000-0002-6357-3848 and Bennett, MI orcid.org/0000-0002-8369-8349 (2018) A critical appraisal of gabapentinoids for pain in cancer patients. Current opinion in supportive and palliative care, 12 (2). pp. 108-117. ISSN 1751-4258

https://doi.org/10.1097/SPC.0000000000000337

Table 2 – Detailed summary of tumour-related pain studies – monotherapy and combination therapy study designs.

First author (year)	Pain type	Intervention arm with total daily dose of drugs	Control arm with total daily dose of drugs	Duration of treatment	Number of patients recruited and completed follow-up	Primary outcome measure	Main result(s)
MONOTHERAPY STUDIES							
Raptis (2014)	NCP: "Definite" NCP based on medical history, symptom descriptors, examination +/- imaging/laboratory examinations + positive DN4 questionnaire score.	Pregabalin 75mg/day, titrated to 600mg/day or achievement of appropriate pain relief. PRN opioid available.	Transdermal fentanyl 25µg/hr, titrated by 25µg/hr, after at least 2-3 days, to 150µg/hr or achievement of appropriate pain relief or emergence of poor tolerability. PRN opioid available.	28 days	Recruited: Pregabalin - 60; Fentanyl – 60 Completed follow-up: Pregabalin - 57; Fentanyl - 49	Proportion of patients achieving ≥30% decrease in VAS pain intensity compared with baseline.	73.3% (95% CI 60.3%-83.93%) of the pregabalin group achieved at least 30% reduction in pain compared with 37% (95% CI 24.5%-50.1%) in the fentanyl group ($p<0.0001$)
Mishra (2012)	NCP: Severe neuropathic cancer pain.	Pregabalin group - Pregabalin weekly titration 150mg/day to 300mg/day to 600mg/day	Amitriptyline group - Amitriptyline weekly titration 50mg ON to 75mg ON to 100mg ON; Gabapentin group - gabapentin weekly titration 900mg/day to 1200mg/day to 1800mg/day; Placebo group - Placebo capsules.	4 weeks	Recruited: Pregabalin - 30; Amitriptyline -30; Gabapentin - 30; Placebo -30 Completed follow-up: Unknown	VAS for average pain score over 7 days on 100mm scale	The VAS pain score was significantly lower for the pregabalin group than the amitriptyline group at week 3, gabapentin group at week 4, and placebo group at week 4. No significant difference between groups at baseline. All groups significantly improved.
COMBINATION THERAPY STUDIES							
Caraceni (2004)	NCP: Pain associated with nerve infiltration or compression (confirmed by imaging) and at least one common neuropathic pain symptoms or sign.	Gabapentin 600mg/day, titrated to 1800mg/day if global pain ≥3 & side effects tolerable. Stable daily opioid ~100mg OME	Placebo – identical capsules dispensed in numbered boxes to match gabapentin group. Stable daily opioid ~100mg OME	10 days	Recruited: Gabapentin – 80; Placebo – 40 Completed follow-up: Gabapentin – 76; Placebo - 39	Average NRS global pain across follow-up period	ITT analysis showed significantly lower pain score in gabapentin group (4.6/10) compared to placebo group (5.4/10). No difference in common neuropathic symptoms between groups.

First author (year)	Pain type	Intervention arm with total daily dose of drugs	Control arm with total daily dose of drugs	Duration of treatment	Number of patients recruited and completed follow-up	Primary outcome measure	Main result(s)
Keskinbora (2007)	NCP: patients reporting burning and shooting pain with NRS≥4/10 (despite opioids) and radiologically confirmed nerve compression or nerve invasion.	Gabapentin – 300mg/day for >60 years old or 900mg/day for <60 years old. Initial doses titrated to max 3600mg/day Plus stable opioid (baseline ~140mg/day OME) Rescue dose = additional dose of gabapentin	Opioid doses increased incrementally until sufficient pain relief achieved (baseline ~140mg/day OME). Rescue dose = additional dose of opioid.	14 days	Recruited Gabapentin – 38; Opioid alone - 37 Completed follow-up: Gabapentin – 31; Opioid alone - 32	Burning and shooting pain intensity 0-10 NRS	Significantly lower burning and shooting pain in gabapentin group compared to opioids alone group on days 4 and 13
Mercadante (2013)	Unclassified cancer pain in advanced cancer patients.	Pregabalin - 25mg/day titrated to 150mg/day in 1 week. Morphine (sustained-release) – 60mg/day.	Morphine (sustained-release) – 60mg/day	Main cohort followed for 4 weeks. Sub-cohort followed for 8 weeks.	Recruited Pregabalin – 35; Opioid alone - 35 Completed follow-up at 4 weeks/8 weeks: Pregabalin – 18/16; Opioid alone – 30/28	Pain intensity 0-10 NRS. Frequency of opioid side-effects.	No differences in pain intensity or side-effect frequency reported between the groups at any time point.
Garassino (2013)	NCP: burning, shooting or lancinating pain episodes, dysesthesia or allodynia, with NRS≥4/10, caused by malignant infiltration or compression	Group A: Patients received fix oxycodone dose, 20 mg/day, plus increasing doses of pregabalin, starting at 50 mg/day.	Group B: Patients received fixed pregabalin dose, 50 mg/day, plus increasing doses of oxycodone, starting at 20 mg/day	14 days	Recruited: Arm A: 38; Arm B – 37 Completed: Arm A: 32; Arm B: 35	Reduction of at least 33% of baseline pain	Arm A: 76.5% patients achieved 33% reduction in pain. Arm B: 63.9% achieved 33% reduction in pain. (0R 1.84, 95% CI 0.65-5.22, p-0.25)
Sjolund (2013)	CIBP: bone metastases with pain NRS≥4/10	Pregabalin dose 100mg/day, titrated to maximum 600mg/day. Stable opioid dose.	Placebo in combination with stable opioid.	14 days	Recruited: Pregabalin – 72; Placebo – 80 Completed follow-up: Pregabalin – 59; Placebo – 59	NRS (0-10) worst pain.	Reduction in worst pain greater in pregabalin group compared to placebo group (-1.53 *vs* -1.23).
Chen (2016)	Unclassified severe cancer pain with pain VAS >7/10	Gabapentin 300mg/day, titrated to max 2700mg/day. Oxycodone titrated until appropriate analgesia achieved (VAS<3).	Oxycodone titrated until appropriate analgesia achieved (VAS<3).	6 months	Recruited: Gabapentin – 35; Opioid alone - 35 Completed follow-up: Gabapentin – 30; Opioid alone - 30	Daily average dose (DAD) oxycontin (oxycodone).	Baseline DAD not reported. No difference at 1 week or 1 month. Lower DAD at 3 and 6 months for pregabalin combined with oxycodone compared to opioid alone.

First author (year)	Pain type	Intervention arm with total daily dose of drugs	Control arm with total daily dose of drugs	Duration of treatment	Number of patients recruited and completed follow-up	Primary outcome measure	Main result(s)
Dou (2017)	NCP: cancer-related or cancer-treatment-related, pain NRS≥4/10, controllable with morphine monotherapy ≥180mg/day, DN4 Questions score ≥4	Pregabalin starting dose 150mg/day titrated to 300mg/day, with sustained released morphine titrated until appropriate analgesia achieved (<4 NRS) for 2 weeks. ONE WEEK WASHOUT Placebo with morphine for 2 weeks.	Placebo with sustained released morphine titrated until appropriate analgesia achieved (<4 NRS) for 2 weeks. ONE WEEK WASHOUT Pregabalin (as per intervention protocol) with morphine for 2 weeks.	14 days	Recruited: Pregabalin/Placebo – 20; Placebo/Pregabalin – 20 Completed follow-up: Pregabalin/Placebo – 20; Placebo/Pregabalin – 20	Minimally effective dose (MED) of morphine.	Significantly lower mean morphine MED during pregabalin treatment periods compared to placebo.
Arai (2010)	NCP: both sharp pain and burning pain, or shooting pain +/- allodynia.	Gabapentin/imipramine group - Gabapentin 400mg/day plus imipramine 20mg/day plus regular opioid (oxycodone SR/fentanyl patch) +/- NSAID	Low dose gabapentin group - Gabapentin 400mg/day. High dose gabapentin group - Gabapentin 800mg/day. Imipramine group - Imipramine 20mg/day. All groups had regular opioid (oxycodone SR/fentanyl patch) +/- NSAIDs	7 days	Recruited: Gabapentin/imipramine - 14; Low dose gabapentin - 14; High dose gabapentin - 12; Imipramine – 12 Completed follow-up: Unknown	NRS total pain score (24hr average intensity)	Gabapentin/imipramine group had significant reduction compared with low dose gabapentin and imipramine groups (p=0.005), but not high dose gabapentin. Final scores 2 vs. 4.5 vs. 4 vs. 5 (comparable at baseline).
Banerjee (2013)	NCP: burning pain, shooting/lancinating pain episodes, dysesthesias or allodynia.	Gabapentin 600mg/day, titrated to 1800mg, plus tramadol 150-200mg	Amitriptyline 25mg, titrated to 100mg, plus tramadol 150-200mg	6 months plus 2 weeks washout period	Recruited: Gabapentin - 48; Amitriptyline – 40 Completed follow-up: Gabapentin - 40; Amitriptyline - 36	VAS pain perception on 10cm scale	Decline in VAS pain score from baseline in both groups, but no statistical difference in VAS pain scores throughout study period.
Fallon (2016)	CIBP: bone metastases with scheduled radiotherapy for pain NRS ≥4/10.	Pregabalin 150mg/day, titrated to max 600mg/day, titration only if NRS <2 decrease and/or if patient preference, plus palliative radiotherapy (8 Gy in 1 fraction or 20 Gy in 5 fractions) plus opioid (undefined)	Placebo (same titration schedule and indications as intervention group) plus palliative radiotherapy (8 Gy in 1 fraction or 20 Gy in 5 fractions) plus opioid (undefined)	28 days	Recruited: Pregabalin - 116; Placebo – 117 Completed follow-up: Pregabalin - 84; Placebo - 93	Proportion achieving treatment response (reduction of ≥2 points in worst pain, accompanied by stable or reduced opioid dose)	No statistical difference between pregabalin and placebo groups achieving treatment response (38.8% vs. 40.2%. p=0.816).

First author (year)	Pain type	Intervention arm with total daily dose of drugs	Control arm with total daily dose of drugs	Duration of treatment	Number of patients recruited and completed follow-up	Primary outcome measure	Main result(s)
Nishihara (2013)	CIBP: Intractable pain due to bone metastases.	Pregabalin group - Pregabalin 150mg/day plus regular opioid (median 60mg/day OME) plus regular NSAID (loxoprofen sodium 180mg/day) plus bisphosphonate (undefined) +/- paracetamol (up to 2400mg/day)	Pregabalin/imipramine group - Pregabalin 75mg/day plus imipramine 10mg/day. Pregabalin/mirtazapine group - Pregabalin 75mg/day plus mirtazapine 15mg/day. All groups had regular opioid (median 55-60mg/day OME) plus regular NSAID bisphosphonate +/- paracetamol (as per intervention protocol)	14 days (withdrawal of pregabalin group at 7 days)	Recruited: Pregabalin - 12; Pregabalin/ imipramine - 12; Pregabalin/ mirtazapine – 13 Completed follow-up: Unknown (withdrawal of pregabalin group at 7 days)	NRS for total pain score	Significant decreases in pain score for all groups from day 1 (comparable at baseline). Decreases in pregabalin/imipramine and pregabalin/mirtazapine pain scores significantly greater than pregabalin group from day 2.

Legend: CI = confidence interval, CIBP = Cancer Induced Bone Pain, DN4 = Douleur Neuropathique 4 (questionnaire), ITT = Intention To Treat, NCP = Neuropathic Cancer Pain, NRS = Numerical Rating Scale, OME = oral morphine equivalent, VAS = Visual Analogue Scale