Review Article

The Evidence for Pharmacologic Treatment of Neuropathic Cancer Pain: Beneficial and Adverse Effects

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Abstract

Context. The prevalence of neuropathic pain in patients with cancer pain has been estimated to be around 40%. Neuropathic pain may be caused by a tumor invasion and is considered as mixed nociceptive-neuropathic pain or caused by an anticancer treatment and considered as purely neuropathic pain. The use of adjuvant analgesics in patients with cancer is usually extrapolated from their efficacy in nononcological neuropathic pain syndromes.

Objectives. In this systematic review, we sought to evaluate the evidence for the beneficial and adverse effects of pharmacologic treatment of neuropathic cancer pain.

Methods. A systematic review of the literature in PubMed and EMBASE was performed. Primary outcome measures were absolute risk benefit (ARB), defined as the number of patients with a defined degree of pain relief divided by the total number of patients in the treatment group, and absolute risk harm (ARH), defined as the fraction of patients who dropped out as a result of adverse effects.

Results. We identified 30 articles that fulfilled our inclusion criteria. Overall, ARB of antidepressants, anticonvulsants, other adjuvant analgesics, or opioids greatly outweighed ARH. There were no significant differences in ARB or ARH between the four groups of medication or between patients with mixed vs. purely neuropathic pain. Because of the low methodological quality of the studies, we could not draw conclusions about the true treatment effect size of the four groups of medications.

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Conclusion. Once a diagnosis of neuropathic pain has been established in patients with cancer, antidepressants, anticonvulsants, or other adjuvant analgesics should be considered in addition to or instead of opioids. J Pain Symptom Manage 2013;■:■−■.

Key Words
Antidepressant, anticonvulsant, adjuvant analgesic, cancer, neuropathic pain, opioids

Introduction

In a large cross-sectional survey among cancer pain practitioners and their patients experiencing cancer pain requiring opioids, the prevalence of neuropathic cancer pain was estimated at 40%.[1] This percentage was confirmed in a recent systematic review.[2] Neuropathic cancer pain may be caused by the tumor itself, for example, spinal epidural metastases, leptomeningeal metastases, and cancer involving a nerve plexus, or associated with the cancer treatment, for example, radiation- or chemotherapy-induced neuropathy. Neuropathic cancer pain caused by the tumor itself usually involves both nociceptive and neuropathic components and, therefore, is called mixed pain, whereas the neuropathic pain caused by the cancer treatment is usually considered as purely neuropathic pain.[3]

According to World Health Organization guidelines, in mixed pain, adjuvant analgesics may be used alongside opioids, whereas in purely neuropathic pain, adjuvant analgesics are proposed as the treatment of first choice.[4] Adjuvant analgesics mainly act through blockade of sodium channels in affected peripheral nerves, decreased spinal glutamatergic nociceptive transmission, enhanced propriospinal inhibition, or enhanced descending inhibition of spinal nociceptive transmission. Examples include tricyclic antidepressants (e.g., amitriptyline), serotonergic and noradrenergic reuptake inhibitors (e.g., venlafaxine, duloxetine, and trazodone), gabapentinoids (e.g., gabapentin, pregabalin), anticonvulsants (e.g., sodium valproate, lamotrigine, levetiracetam, and carbamazepine), *N*-methyl-D-aspartate antagonists (e.g., ketamine, amantadine), and local anesthetics (e.g., flecainide, lidocaine).

Evidence for the efficacy of adjuvant analgesics in neuropathic cancer pain is mainly derived from randomized controlled trials in patients with noncancer neuropathic pain syndromes, such as painful diabetic neuropathy, postherpetic neuralgia, and trigeminal neuralgia.[5] However, a number of studies specifically address the efficacy of adjuvant analgesics and/or opioids in neuropathic cancer pain. In this systematic review, the efficacy of adjuvant analgesics, alone or in combination with the opioids or opioids only, in patients with neuropathic pain caused by the tumor itself or purely neuropathic pain, was evaluated after the PRISMA statement for reporting systematic reviews.[6]

Methods

Search Strategy and Selection Criteria

We searched for the literature indexed in PubMed and EMBASE before August 2012, published in English and describing adult cancer patients receiving oral analgesic medication.

The search strategy used in PubMed was as follows: (((((((neuropathy[ti])) OR ((((neuropathic[ti])) OR (("neuralgia"[MeSH Terms] OR "neuralgia"[ti]))))))) AND (((((((tumours OR tumour OR tumor OR tumors OR carcinoma)) OR ((metastasis OR metastases))) OR (("oncology"[tiab]))) OR ((cancer))) OR ((oncological[tiab]))) OR ((neoplasm)))))) AND ((((((((((drug therapy)) OR ((pharmacological))) OR (("pharmacology"[MeSH Terms] OR "pharmacology"[tiab] OR "pharmacological"[tiab]))) OR ((tricyclic antidepressants))) OR ((anti epileptic agents))) OR ((anti-epileptic agents))) OR ((anticonvulsants))) OR ((opioids OR ketamine OR flecainide)))))) AND ((((((((((randomized controlled trial[pt])) OR ((controlled clinical trial[pt]))) OR ((randomized[tiab]))) OR ((placebo[tiab]))) OR ((randomly[tiab]))) OR ((clinical trials as topic[mesh:noexp]))) OR ((trial[ti]))) NOT