

NEUROPATHIC PAIN – MECHANISMS GUIDE TREATMENT

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The number of trials for peripheral neuropathic pain has expanded greatly in the last few years. These have been summarized in several recent meta-analyses that are referred to in the following (1,4). The treatments discussed below have all been demonstrated to provide statistically significant and clinically meaningful treatment benefits compared with placebo in multiple randomized controlled trials. However, no data are available explicitly for small fiber neuropathies. Therefore, the evidence for painful polyneuropathies in general is summarized. Furthermore, there are no approved drugs for the treatment of small fiber neuropathy in the USA. All medications discussed will be off label. Non-medical treatments, i.e. neurostimulation techniques, psychological therapy as well as physio- and occupational therapy are not the focus of this summary.

Antidepressants

The effectiveness of tricyclic antidepressants (TCAs) in neuropathic pain may account for their broad range of pharmacological actions. These compounds are inhibitors of the reuptake of monoaminergic transmitters. They are believed to potentiate the effects of biogenic amines in CNS pain modulating pathways. In addition, they block voltage dependent sodium channels and alpha adrenergic receptors. Duloxetine which block both serotonin and norepinephrine reuptake (SNRI) was efficacious in diabetic painful neuropathy (DPN).

Anticonvulsants (Ca-channel modulators)

Clinical trials with gabapentin and pregabalin have examined patients with DPN. Besides reduction in pain improvements in sleep and quality of life were also demonstrated. There is growing evidence supporting mechanism of action on the $\alpha 2\delta$ -subunit of neuronal calcium channels partly located at the presynaptic spinal terminals of primary afferent nociceptors. Gabapentin and pregabalin are generally well tolerated and have no drug interactions. These advantages make them a suitable option especially for the elderly, a population very often suffering from several comorbidities that need multiple drug therapies.

Tramadol, opioid analgesics and tapentadol

Tramadol is a norepinephrine and serotonin reuptake inhibitor with a major metabolite that is a μ -opioid agonist. Sustained efficacy for several weeks has been demonstrated for oral tramadol in DPN and in patients with painful polyneuropathy of various causes.

The use of strong opioids for patients with chronic neuropathic pain is highly controversial. To date several positive trials of oral strong opioids in various neuropathic pain entities have been published. Recent German guidelines for long-term opioid use in non-cancer pain state that about 25% of patients benefit from the therapy (6). However, the use of opioids requires caution in patients with a history of chemical dependence or pulmonary disease. It is recommended to use long-acting opioid analgesics (e.g., sustained release preparation or transdermal applications) with a maximal dose of less than 120mg morphine equivalent. Opioids should only be considered when alternative approaches of treatment have failed and should be used in a multimodal setting (6).

Tapentadol functions both as a μ -opioid receptor agonist as well as a norepinephrine reuptake inhibitor, thus MOR-NRI. It has shown efficacy in DPN.

Topical capsaicin

Capsaicin is an agonist of the vanilloid receptor (TRPV1) which is present on the sensitive terminals of primary nociceptive afferents. During application it has an excitatory action, later a prolonged inactivation of the receptive terminals. A single application of 8%-capsaicin patches showed pain relief for up to 3 months in patients with peripheral neuropathic pain.

Treatment recommendations

In summary, the medical management of painful polyneuropathies consists of three main classes of systemic medications ((i) serotonin/norepinephrine modulating antidepressants, (ii) Ca-channel modulating-anticonvulsants, (iii) tramadol, opioids and MOR-NRI and of (iv) a topical medication (capsaicin). A useful way to compare the efficacy of different treatments is the consultation of systematic reviews to determine the best available drugs (4).

Since more than one mechanism is at work in most patients, a combination of two or more analgesic agents to cover multiple types of mechanisms is reasonable. However, the evidence for combination therapy is sparse (5).

Drug-related adverse effects are common in the treatment of neuropathic pain, not only because of the specific medications used but also because many patients with this condition are older, take other medications, and have comorbid illnesses. Therefore, the drugs of first-choice have to be judged on the basis of these data.

Future

Recently, a new classification of peripheral neuropathic pain has been proposed that subgroup patients based on patterns of sensory signs (2). A first trial indicated that a specific medication might be effective in on subgroup and not in the other (3). Thus, stratifying patients based on this new classification might lead to an individualized treatment in neuropathic pain.

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Conflict of interest

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