

AS WITH ANY NEUROPATHIC PAIN SYNDROME, the response to CRPS treatment varies with each patient. Treatment can involve interventional techniques (sympathetic blocks, spinal cord stimulation, analgesics) or medications (adjuvants antidepressants, anticonvulsants, bisphosphonates, muscle relaxants, Beta 2 blockers, local anesthetics, opioids etc.)¹. For patients with poorly-controlled pain at the time of evaluation, opioids should be considered earlier in the treatment plan.

Overview

The use of opioids to treat neuropathic pain is controversial^{2,3}. Arner and Meyerson found that infusions of morphine

long-term opioid use, as well as using both an opioid and an adjuvant in treatment⁽¹⁾. Gilron et al's double-blind clinical trial showed that gabapentin and morphine extended-release are more effective when combined with an opioid individually, suggesting a potential analgesic effect¹².

Methadone

Methadone has received significant attention lately due to its prolonged half-life, potency, and low cost. Methadone works well with μ and δ opioid receptors and blocks the N-methyl-D-aspartic acid (NMDA) receptor, suggesting that it can help manage neuropathic pain when hyperalgesia is present¹³. Randomized

(ECG) should be done initially and after adding these medications.

Tramadol

Another opioid of interest is tramadol, which produces additional analgesic effects by blocking the reuptake of serotonin, a neurotransmitter involved in the control of pain perception, sleep, and mood, and norepinephrine, a neurotransmitter that increases the heart rate, blood pressure, and blood sugar level²¹.

A randomized study of individuals with painful diabetic peripheral neuropathy showed that tramadol relieves spontaneous pain and allodynia more effectively than placebo²². Caution should be used in

The Use of Opioids in CRPS-related Pain

By Ricardo A. Cruciani, MD, PhD

were ineffective in relieving neuropathic pain, but the study was flawed because of selection bias, small sample size, and lack of drug titration^{4,5}. Subsequent evidence suggests that opioids might be effective in treating neuropathic pain. Trials for postherpetic neuralgia demonstrate the analgesic benefits of morphine and oxycodone, while in studies with patients with non-malignant neuropathic pain, a fentanyl citrate injection can provide better relief when compared with diazepam^{6,7,8}. An open study on the use of fentanyl patches showed that few patients achieve lasting pain relief⁹.

A retrospective study of individually titrated opioid infusions in patients with neuropathic pain indicates that pain relief can be achieved, but the ratio of opioid dose to patient response increases in people with neuropathic pain¹⁰. Recently, however, positive effects have been found with

studies are lacking, but many reports suggest promising results with methadone in neuropathic pain¹⁴⁻¹⁸. Dose titration must be done cautiously, since large differences in the tolerance of different patients to methadone can cause drug toxicity¹⁹.

There are also concerns about methadone-induced cardiac toxicity and current literature is not conclusive. Although Krantz et al report a longer QTc interval than normal and Torsade de Pointes—a type of abnormal accelerated ventricular rhythm—with high doses of methadone, others could not confirm these findings¹⁹. It is also suggested that competitors of Cytochrome P450 3A4 (CYP 3A4), an important enzymatic pathway for the disposal of methadone in the body and the Lkr current, a delayed purifying potassium current that allows the cardiac fibers to return to a normal state, could increase methadone toxicity²⁰. In these patients, an electrocardiogram

these patients when antidepressants are added. Selective serotonin reuptake inhibitors (SSRIs) could increase the risk for of a possibly fatal serotonin syndrome if they are mixed with monoamine oxidase inhibitors (MAOIs).

Screening Tools

The fear of drug addiction is probably our biggest concern²³. Several tools have been developed to assess risk factors for drug addiction, including the Opioid Risk Tool (ORT), the Substance Abuse Screening Instrument, and the Prescription Drug Use Questionnaire (PDUQ)²³. These tests help physicians develop risk assessment protocol for their practices and categorize patients according to their risk. Before opioids are started, a careful clinical history should be taken with special emphasis on drug addiction issues and a consultation with an addiction psychiatrist should be considered with high-risk patients²⁴.

Conclusions

These data suggest that although neuropathic pain may be less opioid-responsive than nociceptive pain, effective pain relief can be achieved by finding a dose that works for each patient. The potential for opioid side effects might be higher in patients with neuropathic pain because of the higher opioid doses required to relieve pain. The most common side effects are constipation and sedation, but urinary retention, itching, and respiratory depression are also reported.

Drug tolerance that causes an increase in opioid dosage without disease progression is an argument against opioid use, and could be encountered in patients treated long-term with opioids as well as with short exposure to certain opioids. The strategy to overcoming tolerance is to safely titrate the opioid, to achieve an appropriate analgesic response, or to switching to a different opioid.

The data on the analgesic efficacy of opioids in patients with CRPS are very limited. Some of the underlying mechanisms of CRPS are common to several neuropathic pain syndromes, including postherpetic neuralgia and painful diabetic peripheral neuropathy, which are used most often for studying analgesic efficacy. These similarities justify the assumption of a similar response in patients with CRPS, but controlled trials are necessary to determine the efficacy in this patient population.

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Glossary

Anticonvulsants: medicines used to prevent or treat convulsions (seizures)

Electrocardiogram: test that records the electrical activity of the heart

Hyperalgesia: an enhanced intensity of pain sensation

Nociceptive pain: pain caused by a painful stimulus

Opioid: one of a group of synthetic sedative narcotics like opiates, but increasingly refers to all opium-like narcotics

Painful Diabetic Peripheral Neuropathy: most common complication of diabetes mellitus; a progressive disorder that results in a gradual decrease in peripheral sensation and eventually complete loss of sensation

Postherpetic neuralgia: neuropathic pain condition caused by the varicella zoster virus in a dermatomal distribution (the area governed by a particular sensory nerve) after an attack of herpes zoster; commonly known as shingles

Titration: method for figuring out the concentration of a substance by adding a measured amount of solution, which allows the unknown concentration to be calculated

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