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Review Article

Overview of the Pharmacological Management of Neuropathic Pain

Virendra Yadav^{*}, Manish Singh, Manoj Shukla, Ashish Singh, Virendra Shukla

KRS College of Pharmacy, Gonda, UP, India

ABSTRACT

Neuropathic pain refers lesions or disease affecting the somatosensory nervous system either in the periphery or centrally. Examples of neuropathic pain include painful polyneuropathy, postherpetic neuralgia, trigeminal neuralgia, and post-stroke pain. Clinically, neuropathic pain is characterized by spontaneous ongoing or shooting pain and evoked amplified pain responses after noxious or non-noxious stimuli. neuropathic pain is treated as a 'blanket condition' in this guideline regardless of its aetiologies, unless there is valid and robust clinical and health economics evidence that shows the clinical efficacy and cost effectiveness of a particular treatment for a specific neuropathic pain condition. Management of neuropathic pain requires an interdisciplinary approach, centered around pharmacological treatment. A better understanding of neuropathic pain and in particular of the translation of pathophysiological mechanisms into sensory signs will lead to a more effective and specific mechanism-based treatment approach.

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***Correspondence to:**

Mr. Virendra Yadav

Email:

virendra.rkgit@gmail.com

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INTRODUCTION:

Neuropathic pain refers to pain that stems from an injury to a single nerve or to several nerves in the body. You actually might feel the pain in one or more parts of the body. Neuropathic pain can occur at any age but affects older people more frequently than younger people. [1] Damage to the nerves can change a person's sense of touch and can limit arm and leg movement. Although there are several distinct types of neuropathic pain the three most common are:

1. Postherpetic neuralgia
2. Peripheral neuropathy including diabetic neuropathy
3. Complex regional pain syndrome (CRPS)

Postherpetic neuralgia

Postherpetic neuralgia is a painful condition that can follow the virus known as shingles. Shingles is a painful skin rash and is caused by the same virus that causes chicken pox. [2] Shingles usually develops on the side of the chest and back but can also occur on the forehead, abdomen arms and legs. Postherpetic neuralgia develops if the pain from shingles lasts for more than three months after the rash heals. It may occur at any age but is especially common for people who:

- ❖ Are 50 and over
- ❖ Have other nerve conditions
- ❖ Have immune systems weakened by HIV or other diseases
- ❖ Had a more severe shingles rash

If you have had shingles and if you have experienced a pain that persisted for at least three months after the rash from the shingles healed you may also have developed postherpetic neuralgia. The pain, itching and tenderness will most likely be within several inches of the area of the shingles rash. [1,2,3]

Peripheral neuropathy

Peripheral neuropathy results from an injury or disease that damages the peripheral nerves in the body. These are the nerves that branch away from the brain and spinal cord toward your arms,

legs, hands and feet. Peripheral neuropathy can occur in one or more of these parts of the body. The nerve damage may be due to infection, trauma or diseases such as diabetes. [4,5]

Neuropathic Pain

The most common type of peripheral neuropathy affects people with diabetes. This specific condition is referred to as diabetic neuropathy. This can occur when a person has high blood sugar levels for many years. When uncontrolled blood sugar levels stay high for a long time, damage can occur to the insulation around the nerves (the myelin sheath). This damage can happen with Type 1 or Type 2 diabetes and it can occur at any age. However taller people tend to have more diabetic neuropathy than shorter people. [5] High blood sugar levels tend to damage the longer nerves in taller people. Other factors that contribute to diabetic neuropathy include:

- ❖ High blood sugar levels for many years
- ❖ Alcohol overuse
- ❖ Smoking
- ❖ High blood pressure
- ❖ High blood cholesterol

These behaviors and conditions can also cause you to lose feeling in your feet and this can lead to foot ulcers. It is a good idea to protect and check your feet every day. If anything is wrong with your feet call your doctor or other

medical professional. Here are the symptoms for diabetic neuropathy:

- ❖ Numbness, tingling and burning in the feet and lower legs especially at night
- ❖ Burning, aching and sharp pain in the feet, arms or hands
- ❖ Muscle weakness in the arms, legs, hands and feet

Complex Regional Pain Syndrome (CRPS)

CRPS refers to pain that occurs in the hand, foot or face but can occur in any area of the body. The exact cause of CRPS is not known. Current thinking is that injury to the nerves or emotional trauma starts the pain and then can cause a cycle of suffering, inactivity and disability.[6,7] Here are the symptoms of CRPS:

- ❖ Deep aching, burning, shooting pain or sensitive skin in any area of the body but particularly on the face, hands or feet
- ❖ Swelling or sense of swelling in the affected area
- ❖ Weakness in the affected body part
- ❖ Limited movement in the affected area
- ❖ Temperature or skin color changes to the painful body part
- ❖ Change in mood
- ❖ Extremely sensitive skin
- ❖ Sleep problems

Treatment for neuropathic pain

Research has shown that treatment specifically tailored for you can help you better manage your pain. You will want to discuss all of your options with your medical team to determine what sort of treatment program is right for you. Depending on your specific needs, physicians, psychologists or physical therapists may be involved in your treatment program.[7,8,9]

Treatment of neuropathic pain includes:

- ❖ Increasing physical activity
- ❖ Using cognitive-behavioral strategies and stress management techniques to help with mood and functioning
- ❖ Using medications to help with pain and mood
- ❖ Managing stress
- ❖ Improving your blood pressure
- ❖ Quitting smoking
- ❖ Lowering your blood sugar levels (if you have diabetic neuropathy)

Physical activity

The main goal of treating neuropathic pain is to help improve your comfort in daily life. You may not be eager to be active if you are in pain and feel tired. You may talk with a physical therapist to plan an exercise program to help make you more flexible, fit and make movement more comfortable. The activity should not bring on the pain or make the pain any worse. If you have new or changing patterns of pain or discomfort you should stop the activity.[9] Physical activities such as swimming, water aerobics, walking and biking are the best way to start. Start off slowly but try to increase your activity over time. Try to aim for getting 30 to 60 minutes of exercise most days of the week.

Cognitive-behavioral strategies

Cognitive-behavioral strategies and stress management techniques have been shown to help people better manage and cope with neuropathic pain. The cognitive behavioral approach highlights how thoughts, ideas and beliefs affect your behavior and emotions. In cognitive behavioral therapy

you learn ways to change your thinking styles to decrease suffering. When you increase your ability to cope with the neuropathic pain you are more likely to feel better. Contact your doctor or other medical professional for more information.[10,11]

Medications

Medications are given to decrease pain and discomfort. You may discuss with your medical team which medications you need. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) decrease mild

to moderate pain and inflammation for a short period of time. Medications such as tricyclic antidepressants (TCAs) like amitriptyline, nortriptyline, and desipramine help decrease pain and also help with sleep and mood. Capsaicin and Lidocaine cream may be prescribed to soothe skin sensitivity and relieve pain. Take medications only after consulting with your doctor or nurse practitioner.[12,13]

Pharmacological treatments, key outcomes and analysis

Based on the guideline scope, neuropathic pain is treated as a ‘blanket condition’ in this guideline regardless of its aetiologies unless there is valid and robust clinical and health economics evidence that shows the clinical efficacy and cost effectiveness of a particular treatment for a specific neuropathic pain condition.[14]

It was agreed during the scoping workshop and consultation on the scope and by the Guideline Development Group (GDG) to consider 34 different pharmacological treatments for neuropathic pain within the four main drug classes (antidepressants, anti-epileptics, opioid analgesics and topical treatments). These are listed in table 1. Systematic literature searches were carried out to identify randomised placebo-controlled trials on these 34 different pharmacological treatments for neuropathic pain, as well as any head-to-head comparative trials and combination therapy trials.

Table 1: Pharmacological treatments considered for the clinical guideline on neuropathic pain [7-16]

Drugs classification	Drug
Antidepressants: tricyclic antidepressants (TCAs)	Amitriptyline, Clomipramine, Desipramine, Doxepin, Imipramine, Lofepramine, Nortriptyline, Trimipramine
Antidepressants: selective serotonin reuptake inhibitors (SSRIs)	Citalopram, Fluoxetine, Paroxetine, Sertraline
Antidepressants: serotonin–norepinephrine reuptake inhibitors (SNRIs)	Duloxetine, Venlafaxine
Anti-epileptics (anticonvulsants)	Carbamazepine, Gabapentin, Lamotrigine, Oxcarbazepine, Phenytoin, Pregabalin, Sodium valproate, Topiramate
Topical treatments	Topical capsaicin, Topical lidocaine
Opioid analgesics	Buprenorphine, Co-codamol, Codeine phosphate, Co-dydramol, Dihydrocodeine, Fentanyl, Morphine

First-line treatment

The first-line treatment for people with painful diabetic neuropathy is oral amitriptyline or pregabalin.

For amitriptyline: start at 10 mg per day with gradual upward titration to an effective dose or the person's maximum tolerated dose of no higher than 75 mg per day (higher doses could be considered in consultation with a specialist pain service).

For pregabalin: start at 150 mg per day (divided into two doses; a lower starting dose may be appropriate for some people) with upward titration to an effective dose or the person's maximum tolerated dose of no higher than 600 mg per day (divided into two doses).

For people with painful diabetic neuropathy offer oral duloxetine as first-line treatment. If duloxetine is contraindicated offer oral amitriptyline.

For duloxetine: start at 60 mg per day (a lower starting dose may be appropriate for some people) with upward titration to an effective dose or the person's maximum tolerated dose of no higher than 120 mg per day.[15,16]

Second-line treatment

If satisfactory pain reduction is not achieved with first-line treatment at the maximum tolerated dose offer treatment with another drug instead of or in combination with the original drug after informed discussion with the person.

If first-line treatment was with amitriptyline (or imipramine or nortriptyline) switch to or combine with oral pregabalin.

If first-line treatment was with pregabalin, switch to or combine with oral amitriptyline (or imipramine or nortriptyline) as an alternative if amitriptyline is effective but the person cannot tolerate the adverse effects.[10]

For people with painful diabetic neuropathy

If first-line treatment was with duloxetine switch to amitriptyline or pregabalin or combine with pregabalin if first-line treatment was with amitriptyline switch to or combine with pregabalin

Third-line Treatment

If satisfactory pain reduction is not achieved with second-line treatment: refer the person to a specialist pain service and/or a condition-specific service and while waiting for referral: consider oral tramadol as third-line treatment instead of or in combination with the second-line treatment consider topical lidocaine for treatment of localised pain for people who are unable to take oral medication because of medical conditions and/or disability.[11] For tramadol as monotherapy, start at 50 to 100 mg not more often than every 4 hours, with upward titration if required to an effective dose or the person's maximum tolerated dose of no higher than 400 mg per day. If tramadol is used as combination therapy more conservative titration may be required.[13]

Other treatments

The recommendation for other treatments include: do not start treatment with opioids (such as morphine or oxycodone) other than tramadol without an assessment by a specialist pain service or a condition-specific service.

The pharmacological treatments other than those recommended in this guideline that are started by a specialist pain service or a condition-specific service may continue to be prescribed in non-specialist settings, with a multidisciplinary care plan, local shared care agreements and careful management of adverse effects.

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