



Neuropathic Pain

1. Medical Condition

Neuropathic pain is defined as pain arising from a lesion or any disease that causes dysfunction of the somatosensory system. Neuropathic pain is frequently difficult to treat, and may interfere with everyday activities, recreation and consequently, effective participation in sport. Athletes with underlying neurological conditions or musculoskeletal injury have a higher incidence of neuropathic pain.

Because of these challenges the successful management of neuropathic pain frequently demands a multi-pronged approach comprising pharmacologic and non-pharmacologic treatment options. The primary goal of successfully managing neuropathic pain is to provide symptomatic relief.

Relevant to the TUE process, there are two classes of prohibited substances frequently prescribed to manage neuropathic pain. Both classes are prohibited only in-competition. They are:

- a) Narcotics (“opioid analgesics”)
- b) Cannabinoids (also referred to as “medical marijuana”).

The use of narcotics and cannabinoids in the management of neuropathic pain is often long-term and necessitates regular monitoring. This recognizes the fine balance in titrating a therapeutic, analgesic dose against the potential negative effects, of abuse, dependency, and other co-morbidities. In addition, in certain countries, cannabinoids and/or narcotics remain illegal substances without any recourse to their clinical application and simple possession represents a criminal offence.

2. Diagnosis

A. Medical history

Individuals with neuropathic pain typically have a history of disease or injury to the central or peripheral nervous system. Examples include spinal cord injury and peripheral nerve trauma. Some individuals with stroke or traumatic brain injury may experience central neuropathic pain, often due to thalamic involvement. Individuals with amputations may experience pain from a neuroma in the stump of their residual limb or from “phantom limb” pain, another type of neuropathic pain. Neuropathic pain is also a component of complex regional pain syndrome, often

occurring after central nervous system injury or peripheral trauma. Neuropathic pain tends to be associated with sensations such as numbness, tingling, burning, “shooting” pains, heat and cold, and an “electrical” sensation, although one or more of these symptoms may not be sufficient to establish the diagnosis.

B. Diagnostic criteria

Various questionnaires are available to attempt to distinguish neuropathic pain from nociceptive or peripheral nerve pain. Quantitative sensory testing which analyses perception in response to external stimuli is largely subjective and does not provide conclusive proof of neuropathic pain. A thorough history with evaluation of clinical symptoms, a neurological examination and full sensory testing are necessary to establish an accurate diagnosis. This may be supported by investigations including computerized tomography (CT) and magnetic resonance imaging (MRI), important in evaluating central causes of neuropathic pain. In addition, electromyography (EMG) with nerve conduction studies (NCS) will help to establish or eliminate a peripheral cause of neuropathic pain, mindful that there may be false negatives. The interpretation of these investigations must be made by an appropriately specialised physician.

Due to the complexity of neuropathic pain, the results of relevant investigations should accompany the history, physical examination and treatment in the application for the use of any prohibited substance. The opinion of an appropriate medical specialist will enhance the prospects of a successful application for therapeutic use exemption, particularly where objective findings may not be present.

3. Medical Best Practice Treatment

A. Classes of prohibited substances that may be utilized in the treatment of neuropathic pain:

- 1) Narcotics
- 2) Cannabinoids

Indications:

1. Narcotics

Narcotics maybe used as first-line treatment for acute musculoskeletal injuries and post-operative pain, but these are typically used for a limited period of time, from hours to days. For neuropathic pain, current clinical practice guidelines typically recommend that narcotic analgesics are used as a second-line treatment, or in combination with other classes of medication in the management of chronic, refractory neuropathic pain. Note that some of the

weaker opioids not included in the Prohibited List may be used as first-line agents in specific situations. It should be noted that Narcotics (Section 7) is a “closed” section meaning that only those substances specifically listed are prohibited.

2. Cannabinoids

The most common medical use of cannabinoids is for the management of neuropathic pain. Due consideration and precaution should be exercised in the prescription of cannabinoids, especially for an athlete with a history of substance abuse, psychosis, poorly controlled mood or anxiety disorder.

B. Typical Dosage, Route, Frequency and Recommended Duration of Treatment

1. Narcotics

Narcotics are usually taken orally, but they may also be administered intramuscularly, intravenously, transdermally or via a targeted, intrathecal delivery system.

2. Cannabinoids

Cannabinoids can be taken orally, inhaled through a vaporizer or by smoking.

The dosage and frequency of administration of cannabinoids depends on the quality of the product and need of the individual. The duration of treatment is individualized, and may be indefinite in the case of neuropathic pain due to a chronic injury to the somatosensory system. Regular clinical review by a specialist with expertise in pain management is considered to be the accepted practice to regulate use of pain medications.

4. Alternative Non-prohibited Treatments

There are several classes of medication used in the management of neuropathic pain that are not prohibited. They may be trialled as alternatives to narcotics and cannabinoids.

Amongst these are:

1) Antidepressants such as tricyclic amines and dual reuptake inhibitors of serotonin and norepinephrine (e.g. duloxetine, venlafaxine); calcium channel alpha2-delta ligands (e.g. gabapentin, pregabalin); and topical lidocaine, classified as first-line treatment medications;

2) Tramadol is an “opiate-like” agent that is not prohibited and may be considered as an alternative first-line, or as second-line;

3) Anti-convulsants, mexiletine, N-methyl-D-aspartate receptor antagonists, and topical capsaicin are third-line.

4) Complementary treatments such as acupuncture may also be considered in the management of neuropathic pain.

Given the availability of alternative non-prohibited medications for the management of neuropathic pain, the treating physician should present clear medical justification for the use of narcotics and/or cannabinoids.

5. Consequences to Health if Treatment is Withheld

Chronic untreated neuropathic pain carries the potential to impair a range of activities of daily living from minor to significant, depending on factors including the severity and location of pain, the individual's coping skills and their desired activity level. Medications used to decrease pain can be very helpful in neuromusculoskeletal conditions that impair fundamental activities such as eating, bathing and dressing. Unremitting, chronic pain will also adversely affect the ability to engage in physical activity and sport.

6. Monitoring Treatment

Treatment monitoring is primarily clinical.. The use of narcotics or cannabinoids should be at their lowest effective dose to preserve the functional status of the athlete while minimizing side effects. In certain clinical situations, objective serum measures particularly with narcotic use may be helpful while urinalysis may also provide an adjunct to monitoring cannabinoid use.

7. TUE Validity and Recommended Review Process

In situations including the management of acute pain or in post-operative care, narcotic analgesics may be administered for a period of days to a few weeks. However in the management of chronic neuropathic pain, narcotics and cannabinoids are typically administered long-term. Therefore a TUE may be granted for periods of 1 to 4 years. However an annual review of the status of the athlete-patient by a relevant specialist is recommended to ensure that on-going treatment remains appropriate.

8. Appropriate Cautionary Matters

It is recognized that while these medications may substantially improve an individual's ability to accomplish everyday activities, they may also have a negative impact on the ability to participate effectively in sports requiring dexterity and rapid coordination.

Side effects of narcotics range from drowsiness and lethargy to dependency and even death if they are abused. Cannabinoids carry the potential for unpredictable mood, altered affect, increased anxiety, and diminished concentration, reaction time, alertness, coordination, and judgement. Chronic cannabis smoking has also been shown to carry the same potential for respiratory tract disorder as tobacco smoking.

It may be noted that although the use of narcotic analgesics and cannabinoids may be acceptable from a medical and TUE perspective, the relevant sporting association may decide that in certain situations, the use of narcotics and cannabinoids are an unacceptable safety risk to the athlete and/or other competitors. Sport safety issues are outside the realm of anti-doping.

9. References

1. Chong MS, Brandner B. Neuropathic agents and pain. *New Strategies. Biomedicine & Pharmacotherapy*. 60(7): 318-322. 2006.
2. Collier R. Most Paralympians inspire, but others cheat. *CMAJ*. 179(6): 524. 2008.
3. Davis MP. What's new in neuropathic pain? *Support Care Cancer*. 15: 363-372. 2007.
4. Jongen J, Hans G. Neuropathic pain and pharmacological treatment. *Pain Pract*. 2013
5. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. *Cochrane database of systematic reviews (1469-493X)*, (4), p. CD005454. 2007.
6. <http://www.wada-ama.org/en/World-Anti-Doping-Program/Sports-and-Anti-Doping-Organizations/International-Standards/Prohibited-List/>
7. Dworkin RH, et al. Recommendations for the pharmacological management of neuropathic pain: An overview and literature update. *Mayo Clin Proc*. 85(3)(suppl):S3-S14. 2010
8. Haanpaa M, Treede RD. Diagnosis and classification of neuropathic pain. *Pain: Clinical Updates*. Vol XVIII, Issue 7. 2010
9. Cruccu G, Truini A. Tools for assessing neuropathic pain. *PLoS Med* 6(4): e1000045. doi:10.1371/journal.pmed.1000045. 2009.
10. Marilyn A. Huestis, Irene Mazzoni, Olivier Rabin. Cannabis in sport. *Sports Med*. November 1; 41(11): 949–966.. 2013. doi:10.2165/11591430-000000000-00000.
11. DE Moulin, AJ Clark, I Gilron, et al. Pharmacological management of chronic neuropathic pain – Consensus statement and guidelines from the Canadian Pain Society. *Pain Res Manage* 2007;12(1):13-21
12. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, Nurmikko T. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol* 2010; 17:1113-e88
13. National Institute of Health and Care Excellence. Neuropathic pain - pharmacological treatment. NICE Clinical Guideline 173. 2013