Evidence-Based Practice Group Answers to Clinical Questions

"Naltrexone as Treatment for Neuropathic Pain or Complex Regional Pain Syndrome – 2019 Update"

A Rapid Systematic Review

By

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Clinical Services – Worker and Employer Services

About this report

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About the Evidence-Based Practice Group

The Evidence-Based Practice Group was established to address the many medical and policy issues that WorkSafeBC officers deal with on a regular basis. Members apply established techniques of critical appraisal and evidence-based review of topics solicited from both WorkSafeBC staff and other interested parties such as surgeons, medical specialists, and rehabilitation providers.

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Objective

In 2017, the Evidence-Based Practice Group conducted reviews on naltrexone as treatment for complex regional pain syndrome (CRPS) (June 2017), and neuropathic pain (September 2017). This 2019 review aims to determine whether there is new evidence to support the efficacy and/or effectiveness of naltrexone as treatment for neuropathic pain or complex regional pain syndrome (CRPS).

Methods

- In our previous (2017) systematic reviews investigating the efficacy and/or effectiveness of naltrexone, we found that:
  - There were low level (level of evidence 5), low quality (bias, especially selection bias, and co-interventions cannot be excluded) evidence (from 3 cases) on the effectiveness of low dose naltrexone as an adjunct treatment of patient diagnosed with CRPS (full review can be found in here: ***"link will be added in final copy"***).
  - There was only one case report investigating the effectiveness of naltrexone in treating neuropathic pain (full review can be found in here: http://teamsites/sites/ts_clinicalref/ebpg/Document%20Library1/1/EBPG%20rapid%20review%20-%20Naltrexone%20as%20Treatment%20for%20Neuropathic%20Pain.pdf#search=naltrexone).
- In this 2019 systematic review, we are updating the 2017 systematic reviews by following the same methodology, as follows:
  - A comprehensive systematic literature search was conducted on September 26, 2019.
  - The search was done on commercial medical literature databases, including Cochrane Database of Systematic Reviews® (2005 to September 11, 2019), ACP Journal Club® (1991 to August 2019), Cochrane Clinical Answers® (August 2019), Cochrane Central Register of Controlled Trials® (August 2019), Embase® (1974 to 2019 September 25), Medline Epub Ahead of Print, Medline In-Process & Other Non-Indexed Citations®, Medline Daily Update® and Medline Versions® (1946 to September 24, 2019), that are available via the Ovid® platform.
  - The following combinations of keywords were employed in this search:
    1. For CRPS:
       ((complex regional pain syndrome) **OR** crps **OR** causalgia **OR** (reflex sympathetic dystrophy) **OR** (Sudeck atrophy) **OR** algodystrophy **OR** (post-traumatic vasomotor syndrome) **OR**

(complex regional pain syndrome type 1) **OR** (complex regional pain syndrome type 2) **OR** (complex regional pain syndrome type I) **OR** (complex regional pain syndrome type II) **OR** algoneurodystrophy **OR** (painful post traumatic osteoporosis) **OR** (transient migratory osteoporosis) **OR** (painful post traumatic dystrophy) **OR** (shoulder-hand syndrome)) **AND** naltrexone

2. For neuropathic pain:
   (neuropathic **ADJ** pain) **AND** naltrexone

- Since this review is an update of the previous reviews, the literature searches were limited to those available literature published from 2017 onward. No other restrictions, such as on the language of publication, were implemented in any of these searches.
- A manual search was also conducted on the references of the articles that were retrieved in full.

Results

- Literature search results:
  - Search No. 1 (the application of naltrexone to treat patients with CRPS) identified five[1-5] published studies. Upon examination of the titles and abstracts of these five[1-5] studies, three[3-5] studies were thought to be relevant and were retrieved in full for further appraisal.
  - Search No. 2 (the application of naltrexone to treat neuropathic pain) identified 31[5-35] published studies. Only one[25] published study was thought to be relevant to the objective of this systematic review and was retrieved in full for further appraisal.
- Of the three[3-5] studies that were retrieved in full as the result of search on CRPS, one was in the form of a low quality systematic review[3], one was an expert review[4] and one was a case report[5]. Both review articles[3,4] did not provide any new data and will not be discussed further.
- Wong et al.[5] reported on a case of a 56 year-old woman reporting typical symptoms of CRPS (*but with no formal diagnosis*) due to an ankle fracture, and had been treated with duloxetine, pregabalin, topiramate, physical therapy, non-steroidal anti-inflammatory drugs, and opioids without significant relief of her pain. The authors then added 4.5 mg naltrexone daily to the treatment regiment. The authors reported that within 4 weeks, the patient reported substantial relief from symptoms of pain, allodynia, and function dystonia. The study also reported the patient subsequently received a lower dosage of duloxetine and pregabalin and her symptoms remained adequately controlled for the following 15 months.

- The only study that was thought to be relevant to the application of naltrexone in treating neuropathic pain[25] did not provide relevant data and hence will not be discussed further.

Summary

- This updated review on naltrexone as treatment for neuropathic pain and CRPS did not find any new studies which provided evidence to support its efficacy and/or effectiveness for this application. We found one case report on the application of naltrexone as a co-intervention within a treatment plan, for a patient diagnosed with CRPS-like symptoms. Although this case report provides positive evidence on the potential effect of naltrexone as a co-intervention (*but not as a stand-alone treatment*), it should be noted that potential selection bias (in reporting) cannot be excluded from this study.

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Appendix 1

WorkSafeBC - Evidence-Based Practice Group Levels of Evidence (adapted from 1,2,3,4)

1	Evidence from at least 1 properly randomized controlled trial (RCT) or systematic review of RCTs.
2	Evidence from well-designed controlled trials without randomization or systematic reviews of observational studies.
3	Evidence from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group.
4	Evidence from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments could also be included here.
5	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

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