Evidence-Based Practice Group Answers to Clinical Questions

"Intranasal Ketamine With or Without Intranasal Oxytocin as Treatment for Complex Regional Pain Syndrome (CRPS) and/or Chronic Non-cancer Pain (CNCP)"

A Rapid Systematic Review

By

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Clinical Services – Worker and Employer Services

About this report

Intranasal Ketamine With or Without Intranasal Oxytocin as Treatment for Complex Regional Pain Syndrome (CRPS) and/or Chronic Non-cancer Pain (CNCP)

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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

To determine whether there is any evidence to support the efficacy and/or effectiveness of intranasal ketamine with or without intranasal oxytocin in treating complex regional pain syndrome (CRPS) and/or chronic non-cancer pain (CNCP).

Methods

- A systematic literature review was conducted on May 8, 2018.
- The search was done on commercial medical literature databases, including the Cochrane Database of Systematic Reviews® (2005 to May 2, 2018), ACP Journal Club® (1991 to April 2018), UK York University Database of Abstracts of Reviews of Effects® (1st Quarter 2016), Cochrane Clinical Answers® (April 2018), Cochrane Central Register of Controlled Trials® (March 2018), UK NHS Health Technology Assessment® (4th Quarter 2016), UK NHS Economic Evaluation Database® (1st Quarter 2016), BIOSIS Previews® (1969 to 2008), Embase® (1974 to 2018 May 07), Medline Epub Ahead of Print®, Medline In-Process & Other Non-Indexed Citations®, Medline Daily Update® and Medline® (1946 to May 02, 2018), that are available through Ovid® platform.
- Combination of keywords were employed in this systematic literature search. These keywords included:
    1. ((nasal **ADJ** ketamine) **OR** (intranasal **ADJ** ketamine) **OR** (intra-nasal **ADJ** ketamine)) **AND** ((nasal **ADJ** oxytocin) **OR** (intranasal **ADJ** oxytocin) **OR** (intra-nasal **ADJ** oxytocin)) **0**
    2. ((complex **ADJ** regional **ADJ** pain **ADJ** syndrome) **OR** crps **OR** causalgia **OR** (reflex **ADJ** sympathetic **ADJ** dystrophy) **OR** (Sudeck **ADJ** atrophy) **OR** algodystrophy **OR** (post **ADJ** traumatic **ADJ** vasomotor **ADJ** syndrome) **OR** (complex **ADJ** regional **ADJ** pain **ADJ** syndrome **ADJ** type **ADJ** 1) **OR** (complex **ADJ** regional **ADJ** pain **ADJ** syndrome **ADJ** type **ADJ** 2) **OR** (complex **ADJ** regional **ADJ** pain **ADJ** syndrome **ADJ** type **ADJ** I) **OR** (complex **ADJ** regional **ADJ** pain **ADJ** syndrome **ADJ** type **ADJ** II) **OR** algoneurodystrophy **OR** (painful **ADJ** post **ADJ** traumatic **ADJ** osteoporosis) **OR** (transient **ADJ** migratory **ADJ** osteoporosis) **OR** (painful **ADJ** post **ADJ** traumatic **ADJ** dystrophy) **OR** (shoulder **ADJ** hand **ADJ** syndrome)) **AND** ((nasal **ADJ** ketamine) **OR** (intranasal **ADJ** ketamine) **OR** (intra-nasal **ADJ** ketamine)) **1**
    3. ((complex **ADJ** regional **ADJ** pain **ADJ** syndrome) **OR** crps **OR** causalgia **OR** (reflex **ADJ** sympathetic **ADJ** dystrophy) **OR** (Sudeck **ADJ** atrophy) **OR** algodystrophy **OR** (post **ADJ**

traumatic **ADJ** vasomotor **ADJ** syndrome) **OR** (complex **ADJ** regional **ADJ** pain **ADJ** syndrome **ADJ** type **ADJ** 1) **OR** (complex **ADJ** regional **ADJ** pain **ADJ** syndrome **ADJ** type **ADJ** 2) **OR** (complex **ADJ** regional **ADJ** pain **ADJ** syndrome **ADJ** type **ADJ** I) **OR** (complex **ADJ** regional **ADJ** pain **ADJ** syndrome **ADJ** type **ADJ** II) **OR** algoneurodystrophy **OR** (painful **ADJ** post **ADJ** traumatic **ADJ** osteoporosis) **OR** (transient **ADJ** migratory **ADJ** osteoporosis) **OR** (painful **ADJ** post **ADJ** traumatic **ADJ** dystrophy) **OR** (shoulder **ADJ** hand **ADJ** syndrome)) **AND** ((nasal **ADJ** oxytocin) **OR** (intranasal **ADJ** oxytocin) **OR** (intra-nasal **ADJ** oxytocin)) **0**

4. ((chronic **ADJ** non **ADJ** cancer **ADJ** pain) **OR** ((chronic **ADJ** pain)) **AND** ((nasal **ADJ** ketamine) **OR** (intranasal **ADJ** ketamine) **OR** (intra-nasal **ADJ** ketamine)) **9**
5. ((chronic **ADJ** non **ADJ** cancer **ADJ** pain) **OR** ((chronic **ADJ** pain)) **AND** ((nasal **ADJ** oxytocin) **OR** (intranasal **ADJ** oxytocin) **OR** (intra-nasal **ADJ** oxytocin)) **7**
6. ketamine **AND** oxytocin **AND** ((complex **ADJ** regional **ADJ** pain **ADJ** syndrome) **OR** crps **OR** causalgia **OR** (reflex **ADJ** sympathetic **ADJ** dystrophy) **OR** (Sudeck **ADJ** atrophy) **OR** algodystrophy **OR** (post **ADJ** traumatic **ADJ** vasomotor **ADJ** syndrome) **OR** (complex **ADJ** regional **ADJ** pain **ADJ** syndrome **ADJ** type **ADJ** 1) **OR** (complex **ADJ** regional **ADJ** pain **ADJ** syndrome **ADJ** type **ADJ** 2) **OR** (complex **ADJ** regional **ADJ** pain **ADJ** syndrome **ADJ** type **ADJ** I) **OR** (complex **ADJ** regional **ADJ** pain **ADJ** syndrome **ADJ** type **ADJ** II) **OR** algoneurodystrophy **OR** (painful **ADJ** post **ADJ** traumatic **ADJ** osteoporosis) **OR** (transient **ADJ** migratory **ADJ** osteoporosis) **OR** (painful **ADJ** post **ADJ** traumatic **ADJ** dystrophy) **OR** (shoulder **ADJ** hand **ADJ** syndrome)) **1**
7. ketamine **AND** oxytocin **AND** ((chronic **ADJ** non **ADJ** cancer **ADJ** pain) **OR** ((chronic **ADJ** pain)) **5**

- No limitations, such as on the language or year of publication, were implemented in any of these searches.
- Manual searches were also conducted on the references of studies that were retrieved in full.

Results

- Search results:
    - In search No. 1, there was no published study investigating the combined effect of intranasal ketamine and intranasal oxytocin in treating any conditions. Since there is no published study investigating the combined effect of intranasal ketamine and

intranasal oxytocin, we expanded our literature search parameters.
  - Search No. 2 identified one[1] published study, investigating the efficacy/effectiveness of intranasal ketamine in treating CRPS.
  - There was no published study investigating the efficacy/effectiveness of intranasal oxytocin in treating CRPS.
  - Nine[2-10] published studies investigating the application of intranasal ketamine in treating CNCP were identified.
  - Six[11-16] published studies investigating the efficacy/effectiveness of intranasal oxytocin in treating CNCP were identified in search No.5.
  - Only one[17] published study investigating the efficacy/effectiveness of combined ketamine and oxytocin, administered via any methods, in treating CRPS was identified.
  - Five[18-22] published studies on combined ketamine and oxytocin, administered via any methods, in treating CNCP were identified in search No.7.

  Upon examination of the titles and abstracts of the twenty-two[1-22] published studies identified in this systematic literature search, five[3,4,6,12,13] were thought to be relevant and were retrieved in full for further appraisal. A further five[23-27] published studies were also retrieved in full, resulting from the manual searches on the references of the earlier identified five published studies.

- Of the ten[3,4,6,12,13,23-27] articles that were retrieved in full, none investigated the combined effect of intranasal ketamine and intranasal oxytocin in treating CRPS or CNCP. Further, six[3,6,12,13,24,26] of these ten[3,4,6,12,13,23-27] articles did not provide any data or investigated objectives relevant to this systematic review and therefore these studies will not be discussed further.
- In a small (n=20) randomized cross-over trial (level of evidence 1. Appendix 1) Carr et al.[4] investigated the efficacy and safety of intranasal ketamine for breakthrough pain among patients with chronic pain. Twenty patients with chronic pain (*this study included patients with chronic cancer and non-cancer* pain) and have experienced at least two spontaneous breakthrough pain episodes daily self-administered up to five doses of intranasal ketamine or placebo at the onset of a spontaneous breakthrough pain episode (pain intensity ≥ 5 on a 0–10 scale). Although the authors found that patients reported significantly lower breakthrough pain intensity following intranasal ketamine than after placebo (with pain relief within 10 minutes of dosing and lasting for up to 60 minutes, as well as to the findings that no patient in the intranasal ketamine group required their usual rescue

medication to treat the breakthrough pain episode), these findings must be interpreted cautiously due to the fact that the data were analyzed per-protocol as opposed to per intention to treat (breaking randomization), multiple comparisons were reported in the results and were not accounted for in the study's level 1 error calculations, as well as the reduction in pain level may not be clinically significant (2.6 out 10 among those treated with intranasal ketamine compared to < 1 among placebo).

- Mameli et al.[23] investigated the efficacy of intranasal oxytocin, versus placebo, in treating 14 women with fibromyalgia and comorbid disorders in a double-blind, crossover, randomized trial (level of evidence 1. Appendix 1) for 3 weeks for each treatment. By the end of the study periods, the authors found that, although it was safe, devoid of toxicity and easy to handle, 80 IU a day of oxytocin nasal spray did not induce positive therapeutic effects as measured by visual analog scale of pain intensity, Spielberger State Anxiety Inventory, Zung Self-rating Depression Scale, and SF-12, in this patient population. *It should also be noted that, besides the small number of participants (n=14), this study did not provide any sample size calculation, had multiple primary outcomes and did not take into account the impact co-intervention(s) may have had on the outcomes of interest.*
- A low-moderate quality systematic review (level of evidence 1. Appendix 1) investigating the adverse reactions involving intranasal oxytocin was reported by MacDonald et al.[27]. In this systematic review covering the literature from 1990-2010, MacDonald et al. reported that, among randomized controlled trials studies identified and included in this systematic review, intranasal oxytocin produced no detectable subjective changes in recipients, produced no reliable side-effects and was not associated with adverse outcomes when delivered in doses of 18—40 IU for short term use. The majority of side effects reported, including vertigo, drowsiness, dry mouth or throat, nasal irritation, runny nose, abdominal pain, anxiety, euphoric and/or headache, were reported less frequently by the treatment groups than by the placebo groups.
- An editorial by Bell and Kalso[25] accompanying the study by Carr et al.[4] (summarized above), cautioned that although ketamine is not classified as opioid, it does interact with opioid receptors and is a drug of addiction, with the most popular recreational route being intranasal administration. Bell and Kalso[25] further cautioned that regular use of ketamine is associated with rapid development of tolerance and dependency, and long-term effects of chronic ketamine treatment are still unknown. Further, flashback experiences, hallucinations, memory impairment and psychiatric disorders such as paranoia and schizophrenia are reported to be associated with long-term ketamine

abuse and, perhaps most importantly, the effect of chronic ketamine use on the nasal membrane is unknown. The authors suggested that until the results of long-term data are available, intranasal ketamine should be used with caution and confined to the treatment of problematic cancer-related breakthrough pain.

Summary

- At present, there is no published study investigating the efficacy/effectiveness of combined intranasal ketamine and oxytocin in treating CRPS and/or CNCP.
- At present, there may be some high level low quality evidence on the efficacy/effectiveness of short term intranasal ketamine in treating chronic pain; however this evidence needs to be interpreted with caution due to the quality of the primary study. Additionally, the evidence on intranasal oxytocin as treatment for fibromyalgia, is negative.

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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
5	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

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