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Chronic Pain
(Abstracts)

Contents

Adverse Events in Randomized Controlled Trials of Cannabinoids for Chronic Noncancer Pain

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Introduction: Chronic pain is a highly prevalent condition that is difficult to manage. There has been growing interest in the potential of cannabinoids for chronic pain management, with recent legalisation in both Canada and globally. The current opioid crisis highlights the need for a thorough understanding of both efficacy and safety when prescribing interventions for patients. Thus, there is a significant need to better characterize their risk-benefit profile associated with cannabinoids, particularly in the context of chronic pain.

Objective: To characterize the safety profile of cannabinoids across various intervention subtypes for the management of chronic pain.

Methods: Ethics approval was not applicable because the study did not involve human or animal research. In a recent systematic review, we searched for double-blind, randomized placebo-controlled trials (RCTs) of cannabinoids for chronic noncancer pain in MEDLINE, EMBASE, PsycINFO, CENTRAL and trial registries until June 2018. Cannabinoids administered at any dose or route were included.

Results: 43 RCTs with a total of 4436 participants with chronic pain were included. Pain conditions included central and peripheral neuropathic pain (22), spasticity in multiple sclerosis (13), chronic abdominal pain (2), chronic noncancer pain (2), fibromyalgia (2), chronic headache pain (1) and rheumatoid arthritis (1). AEs experienced in >10% of patients and reported in 2+ trials across intervention subtypes are reported here: smoked cannabis – dizziness, drowsiness,

fatigue, nabiximols – asthenia, dizziness, nausea, fatigue, sublingual/vaporized cannabinoids – euphoria, nabilone – drowsiness, dissociation, dry mouth, weakness, dronabinol – dizziness, headache, euphoria, dry mouth, increased appetite, weakness, drowsiness, depression, diarrhea, nausea, fatigue, oral THC/CBD capsules – asthenia, drowsiness, diarrhea, dizziness, euphoria, fatigue, weakness. Frequency of AE-related withdrawals across intervention subtypes were - sublingual spray THC:CBD (12.5%), synthetic cannabinoids (10.0%) nabilone (9.4%), nabiximols (7.5%), oral THC/CBD capsules (7.0%), dronabinol (6.4%), smoked cannabis (2.3%). Frequency of SAEs across invention subtypes were dronabinol (19.1%), oral THC/CBD capsules (4.4%), nabiximols (3.3%), smoked cannabis (0%), sublingual/vaporised THC (0%), nabilone (0%) compared to placebo (4.7%). Overall, all-cause withdrawals ranged from 8-17% for cannabinoid interventions compared to 0-17% for placebo.

Discussion/Conclusion: Numerous AEs were identified that could adversely impact quality of life and adherence to treatment, with different frequencies and AE profiles across intervention subtypes. The AEs experienced across 3+ subtypes included fatigue, weakness and drowsiness The greatest frequencies of AE withdrawals was associated with sublingual THC:CBD spray, synthetic cannabinoids and nabilone, while the greatest frequency of SAEs was associated with dronabinol, with the remaining subtypes comparable to rates for placebo. The rates of all-cause withdrawals across intervention subtypes were comparable to placebo. These and other harms data may aid clinicians and patients in making informed decisions about cannabinoids for managing chronic pain, particularly in prescribing specific subtypes of cannabinoids for patients with certain sensitivities to AEs.

REFERENCES

1. Blyth FM, Huckel Schneider C. Global burden of pain and global pain policy-creating a purposeful body of evidence. Pain. 2018;159(suppl 1):S43–S48
2. Volkow ND, Baler RD, Compton WM, et al. Adverse health effects of marijuana use. N Engl J Med. 2014;370:2219–2227.
3. Häuser W, Finn DP, Kalso E, et al. European Pain Federation (EFIC) position paper on appropriate use of cannabis-based medicines and medical cannabis for chronic pain management. Eur J Pain. 2018;22:1547–1564

Does the Speed of Sternal Retraction During Coronary Artery Bypass Graft Surgery Affect Postoperative Pain Outcomes?: A Randomized Controlled Trial

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Introduction: Chronic pain is a serious health issue impacting both the quality of life and productivity of patients.[1-3] Chronic post-sternotomy pain (CPSP) is characterized by numbness, severe tenderness on palpation, allodynia, as well as constant pain across the anterior chest wall that can persist for months to years after sternotomy.[4] All patients experience early post-operative pain following coronary artery bypass graft (CABG); unfortunately, approximately 30-40% of CABG patients subsequently develop CPSP.[4-6]

Methods: Ethics approval was obtained from the local REB. The current study is a prospective, double-blinded, randomized controlled trial. A sample size of 316 randomly assigned patients (n=158 per group) was calculated to provide an 80% power at a 2-sided α of 0.05 to detect a 40% decrease in CPSP incidence at 6 months. Eligible patients scheduled for elective, primary coronary artery bypass graft surgery were randomly assigned to either the CONTROL group, in which sternal retraction occurred over 30 seconds (standard practice) or the SLOW group, in which sternal retraction occurred over 15 minutes. Surgical and perioperative anesthesia protocols between the two groups were otherwise the same. Our primary outcome is the incidence of CPSP at 6 months. Secondary outcomes include: CPSP incidence at 3 and 12 months, daily chest pain intensity (NRS scale) at rest and while coughing, daily analgesic consumption, pain quality, quality of life, and pain interference with daily function at 3, 6 and 12 months post-operatively.

Results: To date, 326 patients (n=260 males, n=66 females) have taken part in the study (mean age=65.5 years). A total of 10 additional patients were randomized to account for participants whom did not receive the intervention, were unblinded, lost to follow-up, or expired acutely. Current rates of CPSP in our cohort are 38.2%/27.3%/22.5% at 3/6/12 months follow up, respectively. The following risk factors and confounding variables for chronic post-sternotomy pain were identified in our cohort: previous or active cigarette smokers (n=86), type 2 diabetes mellitus (n=146), atrial fibrillation (n=20), obstructive sleep apnea (n=65), previous myocardial infarction(s) (n=139), previous coronary stenting (n=56), gastroesophageal reflux disease (n=139), chronic obstructive pulmonary disease (n=23), previous cerebrovascular accident(s) (n=14). The following serious adverse events (SAE) have been documented: prolonged post-operative ventilation (>24 hrs) (n=7), stroke (n=4), myocardial infarction (n=2), re-operation (n=5), surgical bleeding (VISION criteria) (n=14), sternal infection (n=12), cardiac failure (n=7), and death (n=8).

Conclusion: The current investigation is near completion, having randomized all 326 patients. Follow-up data collection for the primary endpoint has been collected in all but 35 patients. The incidence of SAE in our cohort is consistent with previous literature in CABG surgery[7-9]. Furthermore, a recent interim analysis for patient safety showed no statistically significant differences in the type or rate of serious adverse events between the two study groups. Preliminary results will follow soon.

REFERENCES:

1. Reitsma, M. L., Vandenkerkhof, E. G., Johnston, S. L., & Hopman, W. M. (2011). Does health-related quality of life improve in women following gynaecological surgery?. *Journal of Obstetrics and Gynaecology Canada*, *33*(12), 1241-1247.
2. VanDenKerkhof, E. G., Hopman, W. M., Goldstein, D. H., Wilson, R. A., Towheed, T. E., Lam, M., ... & Gilron, I. (2012). Impact of perioperative pain intensity, pain qualities, and opioid use on chronic pain after surgery: a prospective cohort study. *Regional Anesthesia & Pain Medicine*, *37*(1), 19-27.
3. VanDenKerkhof, E. G., Hopman, W. M., Reitsma, M. L., Goldstein, D. H., Wilson, R. A., Belliveau, P., & Gilron, I. (2012). Chronic pain, healthcare utilization, and quality of life following gastrointestinal surgery. *Canadian Journal of Anesthesia/Journal canadien d'anesthésie*, *59*(7), 670-680.
4. Steegers, M. A., van de Luijtgaarden, A., Noyez, L., Scheffer, G. J., & Wilder-Smith, O. H. (2007). The role of angina pectoris in chronic pain after coronary artery bypass graft surgery. *The Journal of Pain*, *8*(8), 667-673.
5. Cantero, C., Carolina, G., Matute, P., Tena, B., Rovira, I., & Carmen, G. (2011). Prevalence of postoperative chronic pain after cardia surgery: 14AP2-2. *European Journal of Anaesthesiology (EJA)*, *28*, 193-194.
6. Van Gulik, L., Janssen, L. I., Ahlers, S. J., Bruins, P., Driessen, A. H., van Boven, W. J., ... & Knibbe, C. A. (2011). Risk factors for chronic thoracic pain after cardiac surgery via sternotomy. *European journal of cardio-thoracic surgery*, *40*(6), 1309-1313.
7. Kamel, A. T. H., Hassouna, A., El, H. E. D. A. A., & Hikal, T. S. (2018). Major adverse cardiac events after first time elective isolated coronary artery bypass grafting: A retrospective cohort study. *Journal of the Egyptian Society of Cardio-Thoracic Surgery*, *26*(4), 237-244.
8. Diodato, M., & Chedrawy, E. G. (2014). Coronary artery bypass graft surgery: the past, present, and future of myocardial revascularisation. *Surgery research and practice*, *2014*.
9. Nalysnyk, L., Fahrbach, K., Reynolds, M. W., Zhao, S. Z., & Ross, S. (2003). Adverse events in coronary artery bypass graft (CABG) trials: a systematic review and analysis. *Heart*, *89*(7), 767-772.

Interactions Between Analgesic Drug Therapy and Mindfulness-Based Interventions for Chronic Pain in Adults: A Systematic Scoping Review

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Introduction: Chronic pain is estimated to affect 1.5 billion people worldwide and cost the United States and Canadian healthcare system over $650 billion per year, which exceed the annual costs from cancer and heart disease.[1-3] Given the well-recognized limitations of any one modality of treatment for chronic pain, the evolving concept of multimodal therapy has led to the concurrent use of 2 or more different treatment modalities for chronic pain. Since mindfulness-based interventions (MBIs) and drug therapies likely reduce pain by different mechanisms, their combined use could provide added benefit. However, there have been no reports of interaction effects of the combination of MBIs with any specific analgesic drugs. We conducted this systematic scoping review to describe the landscape of mindfulness-based trials with respect to the drug therapy and evaluate the available evidence on the interaction between MBIs and various pharmacological treatments.

Methods: Ethics approval was not applicable because the study did not involve human or animal research. We searched MEDLINE, EMBASE, CENTRAL, and PsycINFO from inception to July 2019, to identify randomized controlled trials (RCTs) that evaluated the efficacy of MBIs in chronic pain. Two authors screened all studies for inclusion and data was extracted using a form designed for this review. Primary outcomes included: (1) What concomitant analgesic drug therapies (CADTs) the trial participants were receiving; (2) If and how trials controlled for CADTs and analyzed their interaction; and (3) Results of available analyses of the interactions between MBI and CADTs. Secondary outcomes included frequency and severity of adverse events.

Results: Our search identified 848 citations, of which 40 RCTs were eligible for our review. 39/40 MBI trials allowed participants to take CADTs, but only 15/39 of these trials provided any detail of what the CADTs were. Furthermore, only 4/39 trials controlled for CADTs the participants were receiving, and 0/39 trials analyzed the interaction between the MBI and CADTs. No judgment could be made about the safety of MBIs because adverse events were inconsistently reported, with only 9/39 studies reporting any data regarding MBI-associated adverse events.

Discussion: A large body of evidence supports the benefits of MBIs for patients living with chronic pain.[4,5] However, this review demonstrates that more trials investigating the interaction between MBIs and CADTs are needed to better define how MBIs can and should be rationally integrated into patients' multidisciplinary chronic pain management strategy. Additionally, with increasing interest in the potential of MBIs, there is a need to inform risk-benefit considerations. Psychological adverse events are possible during MBIs and thus better harms assessment and reporting are needed in future chronic pain mindfulness trials to characterize the safety profile of MBIs.

REFERENCES:

1. Borsook D. A future without chronic pain: neuroscience and clinical research. *Cerebrum.* 2012;2012:7.
2. Lynch ME. The need for a Canadian pain strategy. *Pain Res Manag.* 2011;16(2):77-80.
3. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain.* 2012;13(8):715-724.
4. Hilton L, Hempel S, Ewing BA, et al. Mindfulness Meditation for Chronic Pain: Systematic Review and Meta-analysis. *Ann Behav Med.* 2017;51(2):199-213.
5. Reiner K, Tibi L, Lipsitz JD. Do mindfulness-based interventions reduce pain intensity? A critical review of the literature. *Pain Med.* 2013;14(2):230-242.

Magnesium for the Management of Chronic Pain in Adults: A Systematic Review

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Introduction: Chronic pain is a highly prevalent and complex health problem that costs the Canadian and United States healthcare system over $650 billion per year, which exceed annual costs from cancer and heart disease.[1,2] High opioid prescribing rates for chronic pain has been associated with increases in opioid-related mortality and misuse disorders, emphasizing the significant need for safer pain management strategies.[3] Emerging evidence supports the safe use of magnesium in controlling chronic pain, but there is no consensus regarding its clinical effects.[4,5] Thus, we conducted a systematic review to assess the current evidence of efficacy and safety of magnesium for the treatment of chronic pain.

Methods: Ethics approval was not applicable because the study did not involve human or animal research. We searched MEDLINE, EMBASE, CENTRAL, and trial registries (ICTPR and ClinicalTrials.gov) from inception to September 2018, to identify randomized controlled trials (RCTs) that evaluated the efficacy of magnesium (at any dose, frequency, or route of administration) compared to placebo in chronic pain. Participants aged 18 years and over reporting any type of chronic pain for at least 3 months were included. Primary outcomes included any participant-reported measures of pain intensity or pain relief that has been previous validated. Secondary outcomes included participants experiencing any adverse event.

Results: Our search identified 1062 citations, of which 9 RCTs containing 418 participants were eligible for our review. Three studies examined neuropathic pain (62 participants), 3 examined migraines (190 participants), 2 examined complex regional pain syndrome (86 participants), and 1 examined low back pain with a neuropathic component (80 participants). Heterogeneity of included studies precluded any meta-analyses. No judgement could be made about safety since adverse events were inconsistently reported. Evidence of analgesic efficacy from included studies was equivocal. However, reported efficacy signals in some of the included trials provide a rationale for more definitive studies. For example, there was some evidence that magnesium may provide some analgesic benefit to people with chronic low back pain with a neuropathic component following 6 weeks of magnesium treatment.[6]

Discussion: For the purposes of routine patient care, there is insufficient evidence to support or refute the hypothesis that magnesium is efficacious and safe in chronic pain. Larger sized trials with good assay sensitivity and better safety assessment and reporting will serve to better

define the role of magnesium in the management of chronic pain. Additionally, due to differing bioavailabilities of various magnesium compounds[7-9], without measuring magnesium levels, it is difficult to determine whether lack of efficacy is due to inadequate dosing or because magnesium is indeed not efficacious. Therefore, these future trials would ideally be stratified by baseline body magnesium levels and magnesium formulations.

REFERENCES:

1. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain.* 2012;13(8):715-724.
2. Lynch ME. The need for a Canadian pain strategy. *Pain Res Manag.* 2011;16(2):77-80.
3. Alford DP. Opioid Prescribing for Chronic Pain--Achieving the Right Balance through Education. *N Engl J Med.* 2016;374(4):301-303.
4. Nechifor M. Magnesium involvement in pain. *Magnes Res.* 2011;24(4):220-222.
5. Herroeder S, Schonherr ME, De Hert SG, Hollmann MW. Magnesium--essentials for anesthesiologists. *Anesthesiology.* 2011;114(4):971-993.
6. Yousef AA, Al-deeb AE. A double-blinded randomised controlled study of the value of sequential intravenous and oral magnesium therapy in patients with chronic low back pain with a neuropathic component. *Anaesthesia.* 2013;68(3):260-266.
7. Firoz M, Graber M. Bioavailability of US commercial magnesium preparations. *Magnes Res.* 2001;14(4):257-262.
8. Kappeler D, Heimbeck I, Herpich C, et al. Higher bioavailability of magnesium citrate as compared to magnesium oxide shown by evaluation of urinary excretion and serum levels after single-dose administration in a randomized cross-over study. *BMC Nutrition.* 2017;3(1):7.
9. Schuchardt JP, Hahn A. Intestinal Absorption and Factors Influencing Bioavailability of Magnesium-An Update. *Curr Nutr Food Sci.* 2017;13(4):260-278.

Nervous Survey II: Persistent Postsurgical Neuropathy in Female Adults after Breast Cancer Surgery

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Background: Recent advances in medicine have seen a significant increase in the population of long-term breast cancer survivors, highlighting the need for knowledge on late postoperative complications.

Persistent postsurgical neuropathy (PPSN), defined as the presence of a new or worsened sensorimotor deficit 3-6 months post-surgery (1), remains a large clinical problem in breast cancer survivors (2,3) with potential for long term disability and psychological distress.

Aims: The primary aim of this study is to establish a baseline prevalence of PPSN in patients at 6 months or later after breast cancer surgery. The secondary aim is to examine if there is any difference in the PPSN prevalence among patients who received perioperative peripheral nerve blocks (PNB) and those who did not.

Methods: After institutional ethics approval, all adult female patients who underwent breast cancer surgery were included from 1/1/2018 to 31/12/2018.

Telephone interviews were conducted at 6 months or later after surgery. Patients were asked if they had experienced pain and/or paraesthesia in relevant nerve/plexus distribution area (surgery site and the same side of body, arm and axillary).

Results: Of the 245 eligible patients, data from 220 patients (230 breasts) were included and analyzed, among which, 50 operative breasts received PNB and 180 did not.

The median follow-up period after surgery was at 14 months (Interquartile Range 13 to 16 months).

The incidence of PPSN was 74% (66% for pain and 28% for paresthesia), of these, those with PNB accounted for 72% (60% for pain and 26% for paresthesia), and without PNB 82% (67% for pain and 29% for paresthesia).

Of concern, 28% PPSN with PNB and 26% without was significant, i.e., moderate to severe.

Conclusions: This study demonstrated that, after breast cancer surgery, PPSN remained a significant late complication in female adults and perioperative nerve blocks played limited role in reducing either the incidence or the severity of PPSN.

REFERENCES:

1. Werner MU, Kongsgaard UE. Defining persistent post-surgical pain: is an update required? *BJA*2014;113(1):1-4.
2. Gärtner R, *et al.* Prevalence of and factors associated with persistent pain following breast cancer surgery. *JAMA* 2009;302(18):1985-92.
3. Mejdahl MK, *et al.* Persistent pain and sensory disturbances after treatment for breast cancer: six year nationwide follow-up study. *BMJ* 2013;346:f1865.