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**Abbreviations used in this issue:**

- CI = confidence interval
- d = differences of standardized mean differences
- DD = developmental delay
- IDDS = intrathecal drug delivery system
- IV-PRN = intravenously-delivered pro re nata (“as required”)
- NRS = numerical rating scale
- OS = overall survival
- PIQ-6 = pain impact questionnaire
- PNCA = nurse/parent-controlled analgesia
- RCT = randomised controlled trial
- TMJ = temporomandibular joint
- VAS = visual analogue scale
- WMD = weighted mean difference

Welcome to the latest issue of Pain Management Research Review.

This month we report some disappointing results for the alleviation of pain and reduction of analgesic prescription using long-term vitamin D supplementation and also a lack of benefit of parent/nurse controlled analgesia (PNCA) over intravenous-delivered “on demand” opioids in children with developmental delay. This study also showed that patients with a basal opioid infusion, as well as PNCA, consumed significantly more opioid than those without a basal infusion.

On a more positive note, 2 meta-analyses show promising results for the use of active psychotherapies such as relaxation or cognitive behavioural therapy for both post-surgical pain and reduced physical impairment. An 11-year observational follow-up study of intrathecal drug delivery systems for refractory malignant pancreatic cancer pain concluded that it is an efficacious treatment and noted no new safety concerns. A review assessing the literature regarding burn-induced pain found a lack of clinical trials investigating the efficacy of analgesics on burn pain whilst another review summarised the current knowledge on allodynic pain mechanisms. We conclude this review by looking at a mouse model of temporomandibular disorder that sheds some light on the underlying mechanisms of the disorder’s development.

We hope you find these and the other selected studies interesting, and look forward to receiving any feedback you may have.

Kind Regards,

Dr Tim Ho

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**Perioperative psychotherapy for persistent post-surgical pain and physical impairment**

**Authors:** Wang L et al.

**Summary:** This systematic review and meta-analysis of randomised controlled trials (RCT) assessed the benefit of various perioperative psychotherapy interventions (independent of active interventions such as physiotherapy) for persistent post-surgical pain (≥2 months) and physical impairment, compared to usual care. A search of Medline, PsyCINFO, CINAHL and the Cochrane Central Registry of Controlled Trials identified relevant RCT trials. Additional studies were identified by screening the reference lists from studies found in Google Scholar, ProQuest Dissertations and Theses Full Text Database and the Cochrane Database of Systematic Reviews resulting in a final count of 15 studies (n = 2220). The studies assessed either active psychological interventions such as relaxation or cognitive behavioural therapy (N = 9) or provision of education and psychological support (N= 7) to reduce pain. The studies included patients who had undergone orthopaedic, coronary artery, bypass graft and colonic and colorectal cancer surgery. At 3-30-months follow-up, education was found to be ineffective at reducing postoperative pain or function. Based on pooled analysis of 8 studies (n = 632) with pain scored on the 10cm visual analogue scale (VAS) and a follow-up of between 3-30 months, 14% more (95% CI 8% more to 21% more) patients who received active postoperative psychotherapy achieved an acceptable pain state (≤3 cm on a 10 cm VAS) compared to usual care and it was concluded that this therapy significantly decreased the intensity of postoperative pain (weighted mean difference (WMD) −1.06 cm, 95% CI −1.56 to −0.55 cm). Similarly, based on pooled analysis of 6 studies (n = 566) active perioperative psychotherapy was found to significantly reduce physical impairment (measured by Oswestry Disability Index) post-operatively [WMD −9.87%, 95% CI −13.42 to −6.32%, risk difference for achieving mild disability (≤20%) 21%, 95% CI 13–29%].

**Comment:** Previous review suggested that depression, anxiety, stress and catastrophisation are associated with worse postoperative pain; however previous trials on perioperative psychotherapy have yielded conflicting results. This is a meta-analysis of 15 RCT showing moderate quality evidence that cognitive behavioural therapy and relaxation therapy, but not education alone, reduce postsurgical pain and physical impairment at 3-30 months. This is despite possible limitation in the training of the personnel delivering the intervention, patient adherence, and pooling different forms of psychotherapy. Cochrane review in 2016 found low quality evidence that preoperative psychotherapy (relaxation technique) reduce postoperative pain, but not education alone. Further study looking at better targeted psychotherapy in the perioperative setting is warranted.

**Reference:** British Journal of Anaesthesia 2018;120(6):1304-14
Association between psychological interventions and chronic pain outcomes in older adults

Authors: Niknejad B et al.

Summary: This systematic review and meta-analysis of randomised controlled trials analysed the efficacy of psychological interventions of cognitive behavioural therapy modalities for the management of chronic (≥3 months) non-cancer pain in elderly patients (mean age ≥ 60 years). 22 studies (n = 2608) were identified from a search of MEDLINE, Embase, PsycINFO, and the Cochrane Library databases. The effect of treatment on outcomes was tested using a mixed-model meta-analysis. Small but statistically significantly improvements were seen with cognitive behavioural therapy in the areas of reduced pain intensity (differences of standardized mean differences (d) = −0.181, P = .006), reduced catastrophizing beliefs (d = −0.184, P = .046) and increased self-efficacy for managing pain (d = 0.193, P = .02). The researchers also found that therapy had the most effect when delivered in a group setting.

Comment: Previous Cochrane review has shown that cognitive behavioural therapy produces small but significant benefits with pain, mood and disability in non-elderly adults with chronic pain. A review by Lunde showed that psychological approaches were moderately effective in pain reduction but not effective on depressive symptom, physical functioning or pain medication use. This is a systematic review of 22 randomized trials of psychotherapy on elderly (mean age ≥60yo), showing a small benefit in pain reduction, catastrophisation and self-efficacy in the short-term which was not sustained at 3 months and 2 years. The main modalities in the studies were behaviour/cognitive coping, cognitive restructuring, behaviour activation, and acceptance. Further study on more robust psychotherapy in our growing aging population is warranted.

Reference: JAMA Internal Medicine 2018;178(8):830-9

Intrathecal drug delivery systems for refractory pancreatic cancer pain

Authors: Carvajal G et al.

Summary: This 11-year observational follow-up study assessed the efficacy of intrathecal drug delivery system (IDDS) for analgesic delivery to treat refractory pancreatic cancer pain at the Institut de Cancérologie de l’Ouest, Paul Papin in France. 93 patients received an intrathecal-placed catheter and an individualised combination analgesic regimen. All were followed from March 2006 to April 2017 (total therapy duration 10,300 IDDS days) with day-hospital visits and telephone calls at least monthly until death. Pain scores (assessed using a numerical rating scale [NRS]) were compared using the Wilcoxon signed rank test. The Kaplan–Meier survival after implantable pump was 91 days, and external pump, 27 days. The patients were behaviour/cognitive coping, cognitive restructuring, behaviour activation, and acceptance. More robust psychotherapy in our growing aging population is warranted.

Comment: Previous Cochrane review has shown that cognitive behavioural therapy produces small but significant benefits with pain, mood and disability in non-elderly adults with chronic pain. A review by Lunde showed that psychological approaches were moderately effective in pain reduction but not effective on depressive symptom, physical functioning or pain medication use. This is a systematic review of 22 randomized trials of psychotherapy on elderly (mean age ≥60yo), showing a small benefit in pain reduction, catastrophisation and self-efficacy in the short-term which was not sustained at 3 months and 2 years. The main modalities in the studies were behaviour/cognitive coping, cognitive restructuring, behaviour activation, and acceptance. Further study on more robust psychotherapy in our growing aging population is warranted.


Efficacy of opioids versus placebo in chronic pain

Authors: Mesko D et al.

Summary: This systematic review and meta-analysis of enriched enrollment randomized withdrawal trials assessed the efficacy of opioids to treat chronic non-cancer pain. A search of MEDLINE and Cochrane trial register databases yielded 15 clinical trials that met the inclusion criteria of ≥10 subjects per arm, double-blind treatment period lasting ≥12 weeks and treatment of any chronic pain condition with any μ-agonist opioids approved for use in the USA. Treatment of pain with opioids resulted in a statistically significant (p<0.001) reduction in pain compared to placebo (standardized mean difference: −0.416), ≥30% and ≥50% improvement in pain (risk difference: 0.166 and 0.137).

Comment: A review published by Choi in 2015 concluded there was insufficient evidence for the efficacy of long term opioid therapy (>3 months) to improve chronic pain and function, however, evidence supports a dose dependent risk for serious harm. This is a meta-analysis of 15 enriched enrollment randomized withdrawal studies which shows efficacy of opioid in chronic non cancer pain for up to 3 months. Enriched enrollment randomized withdrawal studies allow the evaluation of outcome in the open-label titration phase as well. I note the strong placebo effect with 30% pain reduction rate of 63% in the opioid group vs 48% in the placebo group. There was no focus on the risks of opioids or a risk-benefit balance.

Reference: Journal of Pain Research 2018;11:923-4

Monthly vitamin D supplementation, pain, and pattern of analgesic prescription

Authors: Wu Z et al.

Summary: This secondary analysis from the randomized, double-blind, placebo-controlled vitamin D assessment study gives results for the efficacy of monthly high-dose (100,000-IU) vitamin D supplementation on pain and analgesic prescription reduction. The trial randomised 5108 general population members (aged 50-84 years) to monthly capsules of vitamin D3 (n = 2558) or placebo (n = 2550). Pain intensity was assessed using the pain impact questionnaire (PIQ-6) which was administered at baseline, 1 year and at final follow-up (median 3.3 years). Analytic prescription data was collected from the Ministry of Health. No significant difference in mean PIQ-6 scores or proportion of patients dispensed one or more opioids was found. Subgroup analysis found a lower risk of dispensing nonsteroidal anti-inflammatory drugs in vitamin D deficient participants (<50 nmol/L) in the test group compared to placebo (relative risk= 0.87; P = 0.009).

Comment: Vitamin D deficiency is common (based on serum 25-hydroxy vitamin D). Previous observational studies have shown pain conditions were associated with low serum 25-hydroxy vitamin D, but RCT of vitamin D supplement for improving pain showed conflicting results. This is a secondary analysis of a large RCT showing that a monthly dose of 100,000IU vitamin D3 supplement did not result in significant improvement on pain, but is associated with lower risk of NSAID prescription in vitamin D deficient people. Future RCT is warranted for a more definitive answer.

Reference: Pain 2018;159(6):1074-82

The Pain Course: exploring the feasibility of an internet-delivered pain management program when offered by a tertiary pain management service

Authors: Dear B et al.

Summary: This preliminary study reports the feasibility of an internet pain management program (The Pain Course) delivered by the Department of Pain Management at Prince of Wales Hospital, Sydney, Australia. The group conducted a single-group feasibility open-trial design that enrolled 39 patients into the 8-week program. Participants were supported by a clinical psychologist and little clinician support was found to be required (M=71.99min/participant; SD=32.82 min) to achieve high patient satisfaction. Analysis of the entire sample showed some evidence of clinical improvements in depression (avg. improvement=38%; Cohen d=0.74). Improvements were also observed in patients who had clinical levels of difficulties with disability (n=20; avg. improvement=11%; Cohen d=0.64), depression (n=17; avg. improvement=35%; Cohen d=1.24) and anxiety (n=8; avg. improvement=29%; Cohen d=0.57).

Comment: The traditional face to face pain program has limitations, such as cost of attendance, mobility/travel, and waiting list. This is a small prospective cohort study (n=39) showing acceptability and significant clinical improvement in disability, depression and anxiety among patients with significant difficulties in these areas at 3 months. The primary skills taught were: symptom formulation, thought monitoring/challenging, relaxation/pacing, relapse prevention and goal setting. Previous studies have shown that a clinician guided internet based pain program is associated with better engagement and outcome. It would be interesting to see the effect of the internet based program alongside specialist clinic to achieve specific goals such as medication reduction and increase activity level. Further study is warranted.


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Parent/nurse-controlled analgesia compared with intravenous PRN opioids for postsurgical pain management in children with developmental delay

Authors: Czarnecki M et al.

Summary: This randomised controlled trial, conducted at the Children’s Hospital of Wisconsin, Milwaukee, Wisconsin, compared postoperative pain management in children with developmental delays by parent/nurse-controlled analgesia (PNCA) to intravenous opioids delivered on an “as needed” (IV-PRN) basis. Patients (>51, median age =12, 9-15 years, 41% spinal surgery) were randomised into one of 3 groups: PNCA with a basal opioid infusion, PNCA without a basal opioid infusion or IV PRN. Outcome measures investigated were pain scores, opioid consumption and frequency of side effects. At no time point were any between group differences noted in proportions of patients with pain scores <3 vs ≥4. Patients in the PCNA with a basal infusion group consumed significantly more opioid than those in either other group (median = 0.03 mg/kg/h morphine equivalents, 0.02–0.03 mg/kg/h).

Comment: Children with developmental delay are at increased risk for poor pain management. Previous studies have demonstrated safety and efficacy of PNCA for patients unable to operate patient-controlled analgesia independently. This is a small randomized clinical trial comparing PNCA with and without basal rate to IV PRN opioid, showing no difference in pain score. The majority of patients have severe developmental delay and have undergone spinal surgery. The PNCA with basal group consumed significantly more opioid. This is consistent with guidelines that basal infusion may not be necessary or beneficial. Given previous study also suggested lack of improved parent satisfaction associated with PNCA, PNCA may not have an advantage over IV PRN opioid. Further study is warranted.

Abstract

Burn pain: a systematic and critical review of epidemiology, pathophysiology, and treatment

Authors: Morgan M et al.

Summary: This systematic and critical review examines the current literature on the epidemiology, pathophysiology, and treatment of burn-induced pain. A search of Medline yielded 72 articles that met the inclusion criteria on the epidemiology of burn injury and 14 articles on the treatment of burn pain. No articles were found that provided epidemiological data on burn injury pain management outcomes. The authors conclude that there is a very limited number of clinical trials assessing the efficacy of analgesics on burn-related pain and the pathophysiology of burn pain is poorly understood.

Comment: This is a review of literature showing lack of epidemiological data on burns pain management outcome and limited evidence on treatment. Complex peripheral and central nociceptive mechanism and neuronal adaptation has been discussed. Given the variation within burns pain, elucidation of underlying mechanism is important to improvement management. There is a lack of RCT assessing treatment for burns related neuropathic pain. The incidence of chronic pain following burns injury is 25%-36% and is correlated with severity of the injury; but no preventative strategies have been identified in this study.

Abstract

Functional brain imaging: what has it brought to our understanding of neuropathic pain? A special focus on allodynic pain mechanisms

Authors: Peyron R et al.

Summary: This review summarises current research on neuropathic pain with a focus on allodynic pain mechanisms ascertained using functional brain imaging technology. Whilst the spinal cord or brain reorganisation causing this condition are unknown, abnormal or impaired thalamic function and structure have been implicated in neuropathic conditions, including allodynia. Allodynic pain results from an increase in activity in second somatosensory cortex (SII) and in the anterior insular area on the same or opposite side of the body to the pain whereas other neuropathic pain shows bilateral increases in these areas which may result in paradoxical perception. Other information about the connection between pain and these brain areas results from single-case studies involving focal brain lesions.

Comment: This review article summarises functional image finding of brain reorganisation in allodynic pain. Neurpathic pain is associated with bilateral increase in activity in SII and operculo-insular cortex, via thalami; but the how a lesion in the somatosensory pathway leads to these change is unclear. Motor cortex stimulation has shown to change blood flow to brain regions with a high density of opioid receptors; but opioid drugs are known to have a low success rate in neuropathic pain. Further modelling is needed to explain how deafferentation leads to consequential change in areas of increase activity as above, and with regard to both resting state, and dynamic response.

Reference: Pain 2018;157:S67-71
Abstract

Sustained and repeated mouth opening leads to development of painful temporomandibular disorders involving macrophage/microglia activation in mice

Authors: Wang G.Y.F. et al.

Summary: This pre-clinical study out of Canada reports on a novel mouse model of temporomandibular disorder (TMD) that aimed to determine the underlying mechanisms of the disorder. Mouts of mice were kept open to keep in the maximum for 1.5 hours per day for 5 days using a bite block placed between the upper and lower incisors. The animals developed both orofacial allodynia and tempromandibular joint (TMJ) dysfunction. Masseter muscles exhibited dystrophy. Increased F4/80+ macrophages were found in masseter muscles, TMJ posterior synovium and trigeminal ganglia. Microglia activation was also observed in the trigeminal subnucleus caudalis. Orofacial mechanical allodynia, but not TMJ dysfunction, was prevented by the inhibition of macrophage and microglial activation using a colony stimulating factor-1 receptor inhibitor. It was concluded that prolonged periods of mouth opening can contribute to the development of TMD and that underlying mechanisms involve both macrophage and microglia-associated inflammation and the trigeminal system.

Comment: Previous studies have shown an association between prolonged mouth opening and development of chronic TMD. This study by Wang developed a mouse model of TMD by placing a bite block to keep upper and lower incisors maximally open for 1.5 hour/day for 5 days. Immunoassay showed macrophage/microglia activation; and inhibition of macrophage/microglia attenuation hyperalgesia (colony stimulating factor-1 receptor inhibitor). Interestingly, macrophage activation has been observed in the masseter muscle, as well as TMJ synovium. It will be interesting to see if there is altered central processing and associated other somatic symptoms.

Reference: Pain 2018;159(7):1277-88
Abstract

Independent commentary by Dr Tim Ho

Dr Tim Ho is a rehabilitation and pain specialist at Inner West Pain Centre. Tim also works in work capacity centre and addiction medicine. His interests are chronic musculoskeletal pain, neuropathic pain, visceral pain and headache. His research interests are management of comorbid chronic pain and addiction, return-to-work programmes, osseointegration and nursing home resident pain management.

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