Welcome to issue 45 of Pain Management Research Review.

This issue begins with research reporting that yoga was not inferior to standard physical therapy in the management of chronic LBP (low back pain). Another of the papers selected for this issue, focusing on our elderly patients, reported that persistent pain was associated with more rapid memory decline and a greater likelihood of dementia. There is also research suggesting that both pain catastrophising and gender are moderators of the relationship between pain intensity and opioid prescription. This issue concludes with research exploring the mechanisms by which microglia and satellite glial cell activation contribute to the development of neuropathic pain in mice following peripheral nerve injury.

Thank you for all the feedback you have sent—please keep it coming.

Kind Regards,
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Yoga, physical therapy, or education for chronic low back pain
Authors: Saper RB et al.

Summary: Mostly low-income, racially diverse adults with nonspecific chronic LBP (n=320) were randomised to participate in weekly yoga classes for 12 weeks, attend 15 physical therapy sessions or receive an educational book and newsletters in this noninferiority trial. During a maintenance phase, yoga drop-in classes and physical therapy booster sessions were compared with home practice. Compared with physical therapy, Roland Morris Disability Questionnaire and pain scores obtained from the yoga group met the criterion for noninferiority, but yoga was not superior to education for either outcome. Most of the secondary outcomes assessed (pain medication use, global improvement, satisfaction and health-related quality of life) were similar in the yoga and physical therapy groups, and participants from these respective groups were 21 and 22 percentage points less likely to use pain medication at 12 weeks than those in the education group. Improvements among yoga and physical therapy recipients persisted at 1 year with no between-group difference. Adverse events were mostly mild, self-limited joint and back pain and also did not differ significantly between the yoga and physical therapy groups.

Comment: Noninferiority studies are useful when a new therapy is statistically effective as accepted treatment and is reasonable to integrate into clinical practice. This is a 12-week, adequately powered, assessor blinded RCT showing noninferiority of yoga to physiotherapy in a community-based setting for pain and function. The outcome was maintained at 52 weeks. The study population was predominantly lower income patients with nonspecific chronic LBP, and average attendance was seven classes of yoga. Education was provided as a self-care book. The result is consistent with a previous study by Sherman and colleagues. Given that fees for physiotherapy may be prohibitory, especially for patients with lower socioeconomic status, yoga presents an alternative adjunct for multimodal pain management for LBP patients. It would be interesting to see a cost-effectiveness analysis of yoga versus physiotherapy.


Abstract

The pain course: a randomised controlled trial comparing a remote-delivered chronic pain management program when provided in online and workbook formats
Authors: Dear BF et al.

Summary: Individuals requiring pain management were randomised to an internet-based version of the ‘Pain Course’ pain management programme (n=84) or were mailed a workbook version (n=94); both versions of the programme consisted of five core lessons to be undertaken over an 8-week period. Both groups experienced significant improvements in disability, anxiety and depression scores immediately at the end of their programme, but with no evidence of any difference between the two formats. Disability improvements lasted until 3 months postintervention, while the gains for the other primary outcomes were maintained at 12 months. A larger sample size is needed to determine noninferiority. The programme content was the same between the online and workbook formats, including psychoeducation, coping strategies and goal setting. The retention rate was high in the study. A low-tech remotely delivered pain management programme may be a useful alternative. However, it would be interesting to see the subgroup analysis of patients with severe pain and depression, as monitoring and face-to-face contact is likely to be needed.

Reference: Pain 2017;158(7):1289–301

Abstract

Abbreviations used in this issue:

ERAS = enhanced recovery after surgery;
LBP = low back pain;
PDP = Parkinson’s disease;
RCT = randomised clinical trial;
TNF = tumour necrosis factor.

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**Duloxetine 60mg for chronic low back pain**

Authors: Aleix L et al.

Summary: This post hoc analysis of data pooled from four RCTs of duloxetine 60 mg/day (n=642) versus placebo (n=653) for 12–14 weeks in adults with chronic LBP sought to identify predictors of response to the active study drug. Compared with placebo, significantly greater proportions of duloxetine recipients achieved ≥30% and ≥50% reductions in Brief Pain Inventory scores (59.7% vs. 47.8% and 46.6% vs. 35.1%, respectively [p<0.001], particularly among those with early (versus later) improvement (relative risk 2.91 [95% CI 2.30–3.67] and 3.24 [2.44–4.31]) and women (versus men: 1.14 [1.00–1.30] and 1.17 [0.99–1.38]). Response rates did not differ significantly by age, chronic LBP duration or baseline average pain score. Compared with patients with isolated chronic LBP, those with multiple painful sites had greater responses to duloxetine for both ≥30% and ≥50% reductions in Brief Pain Inventory scores (relative respective risks 1.40 vs. 1.07 and 1.51 vs. 1.23).

Comment: Previous phase 3 RCTs have shown efficacy of duloxetine in the treatment of chronic LBP. This is a post hoc analysis of four RCTs of duloxetine 60mg for the treatment of chronic LBP looking at predictive factors for responders. Significant predictors identified were greater level of improvement within the first 2 weeks and greater number of painful body sites. This is consistent with previous studies of duloxetine for other pain conditions and consistent with the descending inhibitory pathway theory. I wonder whether withdrawal symptoms at cessation of duloxetine would be less severe with a time-contingent trial of duloxetine 60mg for 2 weeks (as compared with a longer duration, higher dose trial).


**The effect of a lay-led, group-based self-management program for patients with chronic pain**

Authors: Mehlsen M et al.

Summary: Adults from Denmark with pain of any aetiology and great variation in pain history were randomised to a lay-led version of the CPSMP (Chronic Pain Self-Management Programme) comprising of six 2.5-hour weekly workshops on managing pain in daily life (n=216) or treatment as usual (n=208). CPSMP did not significantly impact it showed no effect on pain-related disability, pain, catastrophisation or self-efficacy at 3 months after the course. This is consistent with a Cochrane review of lay-led patient education programmes for chronic conditions.

Reference: Pain 2017;158(8):1437–45

**Preserved analgesia with reduction in opioids through the use of an acute pain protocol in enhanced recovery after surgery for open hepatectomy**

Authors: Grant MC et al.

Summary: These researchers prospectively collected and analysed data for 60 consecutive patients who underwent open hepatectomy before implementation of an ERAS (enhanced recovery after surgery) pathway and another 120 patients in whom such surgery was performed after the ERAS pathway was introduced. Compared with patients who were operated on pre-ERAS, those who were managed using the ERAS pathway had significantly lower median morphine equivalent requirements at 24 and 48 hours (2.7 vs. 65.0mg and 3.7 vs. 108.0mg, respectively [p<0.001 for both]) but not at 72 hours (1.3 vs. 4.5mg [p=0.56]). Patients treated in the ERAS pathway who received epidurals with increased length of stay, increased fluid requirement and a marginal improvement in analgesia. This observational cohort study showed significant less postoperative opioid use (with similar analgesia and less attenuation of cardiac arrhythmia and improving analgesia; however, recent studies have linked the use of epidurals with increased length of stay, increased fluid requirement and a marginal improvement in analgesia.

Comment: A previous ERAS study demonstrated evidence of epidurals in reducing pulmonary complications, attenuation of cardiac arrhythmia and improving analgesia; however, recent studies have linked the use of epidurals with increased length of stay, increased fluid requirement and a marginal improvement in analgesia. This observational cohort study showed significant less postoperative opioid use (with similar analgesia and less nausea and vomiting), less fluid and a trend toward earlier return of bowel function, and not linked to increased length of stay or fluid use, with the ERAS protocol. In this study, there was a shift of the ERAS paradigm to goal-oriented fluid administration, leading to a significant reduction in overall fluid administration, which allows lower central venous pressure in liver resection patients. The ERAS-epidural protocol was associated with a significantly reduced morphine requirement with less pain in the first 48 hours. A previous rat model has shown that immunomodulatory effects of neuroaxial anesthesia and reduction of perioperative opioids may reduce subsequent tumour burden by 70%. Further study looking at disease recurrence, readmission rates and hospital costs would be interesting.


**Short-duration physical activity prevents the development of activity-induced hyperalgesia through opioid and serotoninergic mechanisms**

Authors: Lima LV et al.

Summary: Murine models were used to test if pharmacological blockade or genetic deletion of µ-opioid receptors modulates excitatory and inhibitory systems in the rostral ventromedial medulla during physical activity. Response frequencies to mechanical paw stimulation, muscle withdrawal thresholds and expression of phosphorylation of the NR1 subunit of the p-NR1 (NMDA [N-methyl-D-aspartate receptor]) and SERT (serotonin transporter) in the rostral ventromedial were assessed. A significant increase was seen in mechanical paw withdrawal frequency and muscle withdrawal threshold was reduced in sedentary mice; the increase in paw withdrawal frequency was prevented by 5 days of wheel-running prior to the model’s induction. Increases in withdrawal frequencies in naloxone-treated and MOR (µ-opioid receptor)/−/− mice were significantly greater than in physically active mice and were similar to sedentary mice. Increased p-NR1 and SERT expression in the rostral ventromedial was observed 24 hours after model induction in the sedentary mice. Increased SERT expression, but not p-NR1 expression, was seen with wheel running. Compared with wild-type physically active control mice, no significant increase in SERT immunoreactivity was noted in physically active, naloxone-treated or MOR/−/− mice. Activity-induced paw and muscle hyperalgesia was reversed in sedentary mice by SERT blockade in the rostral ventromedial.

Comment: Previous mice models have shown that acute bouts of exercise enhance hyperalgesia in sedentary mice, while regular physical activity prevents the development of hyperalgesia; i.e. 5 days for secondary hyperalgesia at the paw and 8 weeks for primary hyperalgesia at the muscle. This mechanistic study using activity-induced pain mice models showed activity-related hyperalgesiamediated, partially, by increased NMDA receptor p-NR1 (increased neuroexcitation) and an increase in SERT (decreased neurotransmission) in the rostroventral medulla; interestingly, short duration exercise (voluntary wheel running versus no wheel in cage) did not alter this p-NR1 change. Furthermore, 5 days of physical activity modulated the above alteration in SERT and activated µ-opioid receptors to reduce secondary hyperalgesia. This may be helpful for psychoeducation and home exercise programmes regarding potential exercise-related central neuromodulation and benefits of graded exposure in exercise load.

Reference: Pain 2017;158(9):1687–710

**Parkinson disease and musculoskeletal pain**

Authors: Lim H-W et al.

Summary: This 8-year retrospective study used Taiwanese health insurance data to compare the incidence and clinical features of musculoskeletal pain between 490 patients aged ≥50 years with newly-diagnosed PD (Parkinson’s disease) and 1960 matched controls without PD; musculoskeletal pain was recorded for 199 patients with PD. Compared with controls, patients with PD had a higher incidence of musculoskeletal pain (adjusted hazard ratio 1.31 [95% CI 1.00–1.68]), and the risk was significantly increased for all sex and age stratifications, with the highest risk seen in middle-aged males with PD followed by older males with PD.

Comment: The prevalence of pain in PD is high at 40–85%, and the pain is most commonly musculoskeletal. This is a population-based 8-year cohort study showing a significantly higher adjusted hazard ratio (1.31) for musculoskeletal pain in patients with PD after adjusting for covariates. The risk is greatest for middle-aged males and is most commonly LBP. Given the different theories on contributors to the higher musculoskeletal pain prevalence, LBP, for example, may be contributed to by stooped posture/osteoartropitic frature, and shoulder pain may be contributed to by rigidity. A secondary analysis also showed a significantly higher prevalence of statin use in the PD population. It will be interesting to see if early intervention, e.g. a pain management programme and/or stopping statins, may improve outcomes and quality of life.

Reference: Pain 2017;158(7):1234–40

Minimum Product Information: ZALDIAR® (tramadol hydrochloride 37.5mg and paracetamol 325mg). Indications: For the treatment of moderate pain.

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References:

PBS Information: This product is not listed on the PBS.
Association between persistent pain and memory decline and dementia in a longitudinal cohort of elders

Authors: Whitlock EL et al.

Summary: The relationship between persistent pain, which may reflect chronic pain, and subsequent cognitive decline was explored in a cohort of 10,065 community-dwelling older adults aged ≥62 years in 2000 and who had responded to pain and cognition questionnaires in both 1998 and 2000. Biennial interviews were conducted, and the data analysis took place in 2016. Persistent pain was present at baseline in 10.9% of the participants, and was associated with worse depressive symptoms and more limitations in activities of daily living. Compared with participants without persistent pain, memory decline in those with persistent pain occurred 9.2% more rapidly, which after 10 years implied 15.9% and 11.8% increased relative risks of inability to independently manage medications and finances, respectively. There was a 7.7% quicker increase in the adjusted probability of dementia, which translated to an absolute 2.2% increase in dementia probability at 10 years among participants with persistent pain.

Comment: Previous study has shown that elderly adults with more severe pain perform poorer on memory tests and executive function. This is a large longitudinal population observational cohort study showing that persistent reports of moderate-to-severe pain is associated with accelerated cognitive decline and increased dementia probability specifically; a 9.2% more rapid decline in memory score and a 12–16% increased risk of inability to manage medications/finances at 10 years. Notably, data on potential confounders such as medication, physical activity and social participation were not available. Giving that a causal relationship is difficult to determine from this study, a mediation analysis may be interesting.


Pain catastrophizing moderates relationships between pain intensity and opioid prescription: nonlinear sex differences revealed using a learning health system

Authors: Sharifzadeh Y et al.

Summary: In this retrospective observational study, data from 1794 adults presenting at a large tertiary-care pain treatment centre were analysed to evaluate relationships between opioid prescription, pain intensity and pain catastrophising. Prescriptions for >1 opioid medication were recorded for 57% of the patients. The authors identified a significant interaction and main effects of pain intensity and pain catastrophising on opioid prescription (p<0.04). Sex differences in the relationships between pain catastrophising, pain intensity and opioid prescription were evident, with opioid prescriptions more common at lower pain catastrophising levels among women compared with men.

Comment: Pain catastrophisation accounts for about 20% of pain intensity. This is a large retrospective study of chronic pain patients showing a significant relationship between pain intensity and opioid prescription; a mediation analysis suggested that pain catastrophising and female sex serve as significant moderating variables, strengthening the relationship between pain intensity and opioid prescription. A prospective, longitudinal study at the time of prescription is needed to establish a causal relationship. However, I wonder if we need to look at treating pain catastrophisation at a lower threshold (e.g. above 20 instead of above 30) in women clinically. It will be also interesting to look at relationships between pain intensity, pain catastrophisation and benzodiazepine use.


IKK/NF-κB-dependent satellite glia activation induces spinal cord microglia activation and neuropathic pain after nerve injury

Authors: Lim H et al.

Summary: Ikkβ conditional knockout mice (Cnp-Cre+/-/Ikkβf/f, cikβf/f) in which IKK/NF-κB-dependent proinflammatory satellite glial cell activation was abrogated, were used to assess the roles of microglia and satellite glial cells in the development of neuropathic pain after peripheral nerve injury. Compared with control mice, these experimental mice exhibited significant attenuation of nerve injury-induced spinal cord microglia activation and pain hypersensitivity, and their expression of nerve injury-induced proinflammatory genes and macrophage infiltration into the dorsal root ganglion were severely compromised. However, there was a minimal effect of macrophages recruited into the dorsal root ganglion on spinal cord microglia activation, indicating a possible causal effect for satellite glial cell activation on spinal cord microglia activation. To determine the molecular mechanisms, Csf1 expression was measured in the dorsal root ganglion. There was amelioration of nerve injury-induced Csf1 upregulation in the cikβf/f mice, suggesting that Csf1 expression was induced in sensory neurons by IKK/NF-κB-dependent satellite glial cell activation.

Comment: Satellite glial cells respond rapidly to peripheral nerve injury and express inflammatory mediators such as TNF-α, in turn, inhibition of TNF-α has an anti-allodynic effect in animal neuropathic pain models. TNF-α was thought to induce the NF-κB/IKKβ transcription pathway to activate microglial cells. This is an animal pain study using an NF-κB knockout mice neuropathic pain model, showing nerve injury-induced satellite glial activation, leading to cytokine colony stimulating-factor 1, which triggers activation of spinal cord microglia. Blockade of satellite glial cell activation in knockout mice attenuated neuropathic pain (mechanical and thermal hyperalgesia) without affecting acute pain sensation. Further research targeting satellite glial cell activation for neuropathic pain is warranted.

Reference: Pain 2017;158(9):1666–77

Commentary

Independent commentary by Dr Tim Ho, who 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.