Pain Management Research Review

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Abbreviations used in this issue:

- MS = multiple sclerosis
- NNT = number needed to treat;
- OR = odds ratio;
- PTSD = post-traumatic stress disorder.

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Welcome to issue 53 of Pain Management Research Review.

Research papers selected for this issue include the impact that legalising cannabis for medical use has had on opioid prescriptions/use in the US, an evaluation of composite responder outcomes of pain intensity and physical function in clinical trials of neuropathic pain, the use of a mobile app in the management of chronic musculoskeletal pain, guidelines regarding the use of onabotulinumtoxin A for chronic migraine, and the contributions of chronic pain among suicide decedents and of opioids in depression among patients with chronic pain.

With the year fast coming to an end, it is a good time to send your feedback regarding this year’s issues, and to offer any suggestions for 2019.

Kind Regards,
Dr Tim Ho
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Dynamic pain connectome functional connectivity and oscillations reflect multiple sclerosis pain

Authors: Bosma RL et al.

Summary: This research investigated the hypothesis that patients with MS (multiple sclerosis) have abnormalities in cross default mode network-salience network static functional connectivity and dynamic functional connectivity in salience network ascending and descending pathways, and disruptions in BOLD variability in the dynamic pain connectome that relate to pain interference and neuropathic pain. To achieve this, questionnaire responses on pain characteristics and interference were obtained from 31 patients with MS and 31 controls, who also underwent resting-state functional MRI to measure static and dynamic functional connectivity and BOLD variability. The findings included: i) neuropathic pain features in about half the patients; ii) salience network-default mode network static functional connectivity abnormalities driven by the mixed-neuropathic subgroup; iii) alterations in how the salience network engages with the ascending nociceptive pathway and descending modulation pathway in patients with mixed neuropathic pain; iv) increased BOLD variability in the default mode network; and v) relationships between pain interference and both the extent of static functional connectivity and BOLD variability abnormalities.

Comment: This is a cohort study (n=31) showing that patients with MS pain have abnormal salience network cross network on functional MRI. Specifically, all MS pain patients had disruptions between the salient network and the ascending pathway (S1). Patients with mixed neuropathic pain (pain DETECT >12) had abnormal cross network connectivity between the salience network (right temporoparietal junction) and the default mode network (posterior cingulate cortex/medial prefrontal cortex), and between the salience network and the descending modulation pathway (PAG). Patients’ pain-related activity interference correlated with the degree of variability in functional connectivity. The right temporoparietal junction (key node of the salience network) facilitates attention to change in sensory input and consequent behaviour responses. Thus when the salience network over-engages with the ascending pathway, the patient has higher pain focus/severity/interference. The default mode network is activated with internal self-referential thought and suppressed with external attention. The abnormal salience-default mode network functional connectivity and activity (BOLD) thus correlates with pain diminishment. This study helps us to further understand functional pain network reorganisation in patients with MS pain. Further research is warranted.

Reference: Pain 2018;159:2267–76

Abstract

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.

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Brain dynamics and temporal summation of pain predicts neuropathic pain relief from ketamine infusion

Authors: Bosma RL et al.

Summary: Thirty patients with refractory neuropathic pain and healthy controls underwent quantitative sensory testing and resting-state functional MRI, completed validated questionnaires and then received intravenous ketamine, with pain assessments conducted 1 month later. Responders (≥30% pain relief, around half of the patients) and nonresponders had respective mean reductions in pain scores of 61% and 7%. Significant associations were seen between both temporal summation and dynamic connectivity before treatment and the effect of ketamine (respectively ρ values ~0.52 and 0.51 [p<0.0001]): the median pretreatment temporal summation and mean pretreatment dynamic connectivity values were significantly higher in responders than nonresponders (400 vs. 4.4 [p<0.001] and 0.55 vs. 0.51 [p=0.006], respectively). The relationship between pretreatment pain facilitation and pain relief was significantly mediated by dynamic engagement of the descending antinociceptive system.

Comment: This is a prospective cohort study of patients with refractory neuropathic pain (n=30) receiving intravenous ketamine infusions (0.5–2 mg/kg/h for 6 hours per day for 5 days) showing that the magnitude of temporal summation and dynamic engagement of descending pain modulation predict treatment efficacy. Dynamic functional connectivity between the default mode network (posterior cingulate cortex plus medial prefrontal cortex) and the descending antinociceptive pathway (PAG), based on functional MRI data, using a dynamic conditional correlations method, was previously validated. High dynamic functional connectivity values suggest fluctuations in connectivity, which reflect greater capacity to decouple attention and perception. This may be a step forward in study methodology for personalised pain treatment. Further study is warranted.

Reference: Anesthesiology 2018;129:1015–24

Abstract

Medical cannabis legalization and opioid prescriptions: evidence on US Medicaid enrollees during 1993–2014

Authors: Liang D et al.

Summary: The impact of medical cannabis legalization in the US on opioid use was explored in a secondary analysis of state-level drug utilisation data covering the period 1993–2014. Medical cannabis legalization reduced the number of Schedule III opioid prescriptions by 29.6% (p=0.03) and their dosage by 29.9% (p=0.02) and also reduced associated Medicaid spending by 26.8% (p=0.04). The researchers did not uncover any evidence to support associations between medical cannabis legalization and Schedule II opioid prescriptions. No association was seen between permitting medical cannabis dispensaries and either Schedule II or III opioid prescriptions after controlling for medical cannabis legalization. For the scenario of all states legalising medical cannabis by 2014, the reduction in annual spending on opioid prescriptions by Medicaid was estimated to be 17.8 million dollars.

Comment: This is an association study (time-series regression analysis) of 1993–2014 Medicaid data (care penetration up to 70%) showing that medical cannabis legalization was not associated with any reduction in Schedule II opioids (e.g. hydrocodone and oxycodone), despite it being associated with a 30% reduction in Schedule III opioids (e.g. codeine). I note that Schedule II opioids account for 95% of all opioid prescriptions in the data. As the legalisation occurred in the late 1990s and early 2000s, the data span before and after legalisation. Twenty-three states have legalised medical cannabis and 27 states have no legalisation. This finding raises the question about previous studies suggesting medical cannabis legalization was associated with considerable reductions in opioid-related adverse outcomes. However, population aggregate data do not reflect individual physician or patient behaviours in response to the legalisation policy. Further research is warranted.

Reference: Addiction 2018;113:2060–70

Evaluation of composite responder outcomes of pain intensity and physical function in neuropathic pain clinical trials

Authors: Patel KV et al.

Summary: This ACTTION individual patient data analysis evaluated composite outcomes associated with duloxetine, gabapentin and pregabalin in nine trials of 2287 patients with painful diabetic peripheral neuropathy and in six trials of 1513 patients with postherpetic neuralgia. There were small correlations between changes from baseline in pain intensity and physical function after treatment in the diabetic peripheral neuropathy trials (p=0.22 [p<0.001]) and no significant correlations for these outcomes in the postherpetic neuralgia trials (p=0.05 [p=0.08]). Assay sensitivities of ten composite outcomes in a subgroup of random patients from the pregabalin peripheral neuropathy and postherpetic neuralgia revealed that a ≥50% improvement in pain intensity, or a ≥20% improvement in pain intensity and a ≥30% improvement in physical function, was significantly associated with pregabalin versus placebo in both development and validation cohorts for both pain conditions. Cross-validation of this composite outcome in trials of gabapentin for postherpetic neuralgia and duloxetine for diabetic peripheral neuropathy revealed a slightly lower NNT than the standard responder outcome of a ≥25% reduction in pain intensity.

Comment: Previous studies on neuropathic pain medication have physical function measured as a secondary outcome, but physical function is a core outcome in clinical trials, as recommended by MIMPACT. This is a validation study looking at ten composite outcomes in neuropathic pain trials, integrating pain intensity and physical functioning, suggesting a composite responder of a ≥50% reduction in pain intensity, or a ≥20% reduction in pain intensity plus ≥30% improvement in physical function. The validation was based on a previous study for pregabalin, duloxetine and gabapentin. I note that relative to the standard responder of a ≥50% pain reduction, this composite outcome produced a slightly better NNT. The physical function data were drawn from the SF-36 physical function subscale, which may not be sufficient. However, a composite responder outcome of pain intensity and physical function may better capture the benefit of neuropathic pain treatments. Further prospective validation study is warranted.

Reference: Pain 2018;159:245–54

Low- and high-threshold primary afferent inputs to spinal lamina III antenna-type neurons

Authors: Fernandes EC et al.

Summary: Whole-cell recordings in a rat spinal cord preparation with attached dorsal roots identified nine antenna cells from a large sample of bicynchonin-filled lamina III neurons (n=66). Intensive branching in laminae III–IV was seen in axon of antenna cells, and in half of the cases there were dorsally directed collaterals that reached lamina I. Tonic and rhythmic firing patterns were detected in the antenna cells, with single spikes followed by hyperpolarisation or depolarisation. The neurons received monosynaptic inputs from low-threshold Aβ and Aδ afferents, along with high-threshold Aβ and C afferents. On selective activation, monosynaptic and polysynaptic excitatory post synaptic potentials driven by C fibres were strong enough to evoke neuronal firing.

Comment: Previous studies have been focused on projection neurons; our understanding of the intrinsic spinal neuron/network is limited. This is basic science research of lamina III antenna type neuron patch clamp recordings in an isolated spinal cord preparation showing monosynaptic inputs from low- and high-threshold afferents, with abundant high-threshold Aδ and C afferent input. Antenna neuron firing is tonic. Immunohistochemistry showed dendrite trees spanning from lamina I to lamina IV, with branching axons spanning from lamina I to lamina VII. This suggests that antenna neurons may function as wide dynamic range neurons and relay input from low-threshold Aβ fibres in lamina III to lamina VII. This may help us further understand pathological conditions such as allodynia where tactile and nociceptive pathways communicate. Further research is warranted.

Reference: Pain 2018;159:2114–22

Chronic pain among suicide decedents, 2003 to 2014

Authors: Petrosky E et al.

Summary: The prevalence of chronic pain among 123,181 suicide decedents who died during the 2003–2014 period was evaluated in this retrospective analysis of US violent death data. Evidence of chronic pain was detected for 8.8% of the suicide decedents, with an increase from 7.4% in 2003 to 10.2% in 2014. However, the authors also noted the limitation that due to the nature of the data and how they were captured, the actual proportions of suicide decedents with chronic pain were likely to be greater. Firearm-related injuries were the cause of death for 53.6% of the suicide decedents, while 16.2% were caused by opioid overdose.

Comment: This is a retrospective analysis of National Violent Death Reporting System data (n=123,181, 18 states) in the US showing that about 9% of suicide decedents had documentation of chronic pain in their incident report, and the percentage increased with time. Interestingly, 53% of decedents with chronic pain died of firearm-related injuries and 16.2% by opioid overdose. The most common types of chronic pain were back pain, cancer and arthritis pain. This study highlights the impact of chronic pain on quality of life and premature death. Among decedents with chronic pain, a history of suicidal thoughts, plans, attempts and intent were common, suggesting opportunities for intervention, particularly for patients with comorbid mental health conditions.


Abstract
Before prescribing, please review the Product Information available at www.seqirus.com.au/PI

MINIMUM PRODUCT INFORMATION: PALEXIA SR (tapentadol hydrochloride)

INDICATION: Moderate to severe chronic pain unresponsive to non-narcotic analgesia.

CONTRAINDICATIONS: Known hypersensitivity to tapentadol or any component of PALEXIA SR; conditions in which mu-opioid receptor agonist activity is contraindicated e.g. significant respiratory depression and acute or severe bronchial asthma or hypercapnia, confirmed or suspected paralytic ileus, acute intoxication with alcohol, hypnotics, centrally acting analgesics or psychotropics; patients who are receiving MAO inhibitors or who have taken them within the last 14 days. PRECAUTIONS: Monitor for signs of abuse and addiction; repeated administration may lead to tolerance; withdrawal symptoms could occur after abrupt discontinuation; not recommended in patients with increased intracranial pressure, impaired consciousness, or coma and severe renal or severe hepatic impairment; caution in patients with impaired respiratory functions, patients with head injury, brain tumours, a history of seizures or any condition that increases risk of seizures, moderate hepatic impairment or biliary tract disease, including acute pancreatitis. Use in pregnancy (Category C). Should not be used during breastfeeding.

INTERACTIONS: Care should be taken when combining with mixed opioid agonist/antagonists or partial mu-opioid agonists; additive CNS depression with concomitant administration of other mu-opioid receptor agonist analgesics, general anaesthetics, phenothiazines, other tranquilisers, sedatives, hypnotics or other CNS depressants (including alcohol and illicit drugs) – reduction of dose of one or both agents should be considered; contraindicated in patients who are receiving MAO inhibitors or who have taken them within the last 14 days; isolated case reports of serotonin syndrome when used in combination with serotonergic drugs (see full PI).

ADVERSE EFFECTS: Very common (≥1/10): dizziness, somnolence, headache, nausea, constipation; Common (≥1/100 to <1/10): Decreased appetite, anxiety, depressed mood, sleep disorder, nervousness, restlessness, disturbance in attention, tremor, muscle contractions involuntary, flushing, dyspnoea, vomiting, diarrhoea, dyspepsia, pruritus, flushing, sweating, change in body temperature, mucosal dryness, oedema. Postmarketing: suicidal ideation, angioedema, anaphylaxis and anaphylactic shock.


PBS Information: Restricted benefit. Chronic severe disabling pain not responding to non-narcotic analgesics. Authority required for increased maximum quantities and/or repeats. Refer to PBS schedule for full restricted benefit and authority information.

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Effect of mobile device-supported single-patient multi-crossover trials on treatment of chronic musculoskeletal pain

Authors: Krawitz RL et al.

Summary: Patients with chronic musculoskeletal pain ≥6 weeks duration who owned a smartphone or tablet with a data plan were randomised to an n-of-1 intervention that featured use of an app (mobilehealth) reminding users to take their treatments as assigned and collecting and uploading daily question responses on pain and treatment- and adverse effects (n=108) or usual care (n=107). Both groups reported reductions in pain-related interference at 6 months of follow-up, with no significant between-group difference (p=0.09). There were also no significant between-group differences for secondary outcomes, with the exception of greater medication-related shared decision making at 6 months (p=0.01). Eighty-eight percent of participants assigned to the app agreed that it could assist other individuals like them to manage their pain.

Comment: This is a randomised, individually designed, single patient, multi-crossover n-of-1 trial comparing individualised pain management regimens using a mobile health app (n=108) with usual care (n=107), showing no significant difference in pain-related interference at 6 months. The app provided reminders of designated treatment on assigned days and collected answers to daily questions. The clinician-patient dyad was predominantly medications based. Surprisingly, short-acting opioids were included as one of the options, and complementary treatment and exercise were lumped into one category. Despite the increased need for subject engagement and risk of attrition, most n-of-1 patients were diligent about reporting daily symptoms. Whereas parallel-group randomised clinical trials estimate average group effects, n-of-1 crossover studies estimate individual participant treatment effects, which may better reflect personalised therapy. It may facilitate future research on patient-centred care. Further research on identifying patients likely to benefit from n-of-1 trials or clinician guided self-experimentation is warranted.


Guideline on the use of onabotulinumtoxin A in chronic migraine

Authors: Bendtsen L et al.

Summary: This consensus statement from the European Headache Federation outlined the recommendations compiled by an expert group regarding onabotulinumtoxin A use for chronic migraine. Onabotulinumtoxin A was described as an effective and well-tolerated treatment for chronic migraine to be used preferably after 2–3 other migraine prophylactic agents have been trialled. Whenever possible, patients should be withdrawn from any previously used medication before starting onabotulinumtoxin A. Onabotulinumtoxin A should be administered at doses of 155–195U injected to 31–39 sites every 12 weeks. Nonresponse should be defined as a <30% reduction in headache days per month during onabotulinumtoxin A treatment, although other factors (e.g. headache intensity, disability, patient preference) should also be considered. If nonresponse is evident after 2–3 treatment cycles, onabotulinumtoxin A should be discontinued. To evaluate response during ongoing onabotulinumtoxin A treatment, the 4-week periods before and after each treatment cycle should be compared. It is recommended that onabotulinumtoxin A is discontinued in patients who experience <10 fewer headaches by day each month over 3 months, with re-evaluation 4–5 months later to ensure that chronic migraine has not recurred.

Comment: This guideline provides recommendations to key questions on the clinical use of onabotulinumtoxin A for chronic migraine based on expert opinion (seven members in the expert panel) and available evidence from prospective studies (27 studies). Only the question regarding efficacy and tolerability can be answered based on scientific evidence. The recommendation regarding the definition of refractory patients (failed 2–3 migraine prophylactics, nonresponders (<30% reduction in headache days after 2-3 treatment cycles), preference for prior detoxification (to address the medication overuse component) and timing for treatment tapering (<10 headaches per month for 3 months) are all based on expert opinion. Further studies are needed.

Reference: J Headache Pain 2018;19:91

Do post-traumatic pain and post-traumatic stress symptomatology mutually maintain each other?

Authors: Ravni SL et al.

Summary: This systematic review of seven eligible cross-lagged studies (of acceptable quality and with moderate risk of bias) on pain and PTSD (post-traumatic stress disorder) symptomatology evaluated the evidence for longitudinal reciprocity and potential bidirectional symptoms in patients with chronic pain and PTSD symptomatology across time. Inconsistent, thereby failing to uniformly support the theoretical framework of mutual maintenance; ii) suggested that hyperarousal and intrusion symptoms may be particularly important for these cross-lagged relationships; and iii) provided inconclusive evidence of catastrophizing as a mediator.

Comment: A previous meta-analysis reported a prevalence of self-reported PTSD of 20% in the chronic pain population. This is a systematic review using autoregressive cross-lagged modelling showing both bidirectional and unidirectional associations between PTSD symptomatology and pain over time, partially suggesting potential mutual maintenance. Significant cross-lagged coefficients between PTSD and pain were assessed based on reported P values in the studies. There is a moderate risk of bias related to performance, attrition and detection, confounders and statistics, due to the small number and heterogeneity. Further study is warranted.

Reference: Pain 2018;159:2159–69

Depression in chronic pain: might opioids be responsible?

Authors: Mazzereeuw G et al.

Summary: This was a brief review of the emerging evidence regarding the contribution of opioids to the development of depression, showing that such an association satisfies many classic elements of causal inference. The authors discussed evidence of associations between opioid use and depression, including opioid dose dependency and duration of use, their role in failure of antidepressants, and the notion that reducing opioid doses may improve depressive symptoms. The clinical implications of known and emerging evidence were also reviewed.

Comment: Previous study has suggested that opioid use is associated with changes in k receptor signal, serotonin/dopamine transmission and grey matter volume of mood centres. This is a topical review of current evidence on depression in chronic pain and depression. There are two longitudinal studies (n=113,997) identifying associations between commencing opioids and later new/recurrent depressive episodes (ORs 1.35–2.17); one cross-sectional study showed an increased risk of depression with higher doses of opioids (OR 2.6). A retrospective cohort study (n=6169) showed an association between longer duration of opioid therapy and treatment-refractory depression. This further adds to the evidence of a list of potential harms from chronic opioid therapy, particularly at high doses. A retrospective cohort study (n=2621) showed antidepressant adherence (treatment of depression) is associated with greater opioid cessation. A small case series suggested that a gradual dose reduction of high-dose opioids was associated with a decrease in depressive symptom severity, with no increase in pain intensity. Further prospective studies are needed at whether opioid taper is associated with reversal of depression and whether treatment of depression facilitates opioid taper are warranted.

Reference: Pain 2018;159:2412–5