Welcome to issue 54 of Pain Management Research Review.

To begin the first issue for 2019, data from three RCTs of the humanised monoclonal antibody galcanezumab for treating episodic or chronic migraine have been analysed and reported, focussing on the impact of continued treatment among participants who did not achieve an optimal early response. This is followed by the presentation of ≤2-year data from an Australian RCT of the internet-delivered pain management programme the Pain Course, which offers varying levels of clinician support. Betulinic acid, extracted from Hyptis emoryi (a desert lavender plant), has been studied and found to offer broad-spectrum biological and medicinal properties that could have potential as a natural nonopioid treatment for chronic pain. This issue concludes with an analysis of US prescription drug monitoring programme data alerting physicians to escalating opioid dosage patterns as an important indicator of increased mortality risk, particularly in patients with OUD (opioid use disorder).

I hope you enjoy this issue and, as always, I invite you to send me your comments and feedback.

Kind Regards,
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Analysis of initial nonresponders to galcanezumab in patients with episodic or chronic migraine

Authors: Nichols R et al.

Summary: This was a post hoc analysis of data from three RCTs comparing galcanezumab with placebo, focussing on continued galcanezumab treatment in participants with episodic or chronic migraine who did not achieve ‘good’ early improvement within 1 month of treatment (episodic, n=450; chronic, n=306). Among participants with episodic migraine, the respective ‘good’ and ‘better’ response rates with continued treatment for those with a ‘modest’ early improvement were 62% and 20%, and the respective rates for those with chronic migraine were 38% and 13%. ‘Good’ responses to continued treatment were also seen for participants who had ‘limited’ (episodic migraine only) or ‘minimal/no’ (both migraine types) early improvement and also for those with episodic migraine who initially experienced worsening. Response patterns for participants who failed to achieve a ‘good’ response within 2 months were similar, but the proportions were lower.

Comment: Galcanezumab is a humanised monoclonal antibody that binds to the CGRP (calcitonin gene-related peptide) receptor and blocks its activity, without blocking the receptor. Three phase 3 RCTs (EVOLVE-1, EVOLVE-2, REGAIN) showed that the responder rates were higher in treatment groups (galcanezumab 120mg and 240mg per month) than the placebo groups. In these studies, a group of late responders was noted, but the rate is unclear. This is a post hoc analysis of these RCTs (n=879 for episodic migraine, and n=555 for chronic migraine) showing subthreshold responders (especially modest responders, or 30–50% fewer migraine headaches) at 1–2 months had a chance (17–60%) of achieving a clinically meaningful response (≥50% reduction in migraine headache days in episodic migraine and ≥30% reduction in chronic migraine) with continued treatment with galcanezumab at 3–6 months. The post hoc nature of the analysis is an intrinsic limitation. Further longer-term clinical trials are needed to clarify this trend of response.

Reference: Headache 2019;59:192–204

Abstract

The Pain Course: 12- and 24-month outcomes from a randomized controlled trial of an internet-delivered pain management program provided with different levels of clinician support

Authors: Dear BF et al.

Summary: These authors reported 12-month and 24-month follow-up for 379 participants enrolled in an RCT comparing three arms that included The Pain Course, an internet-delivered pain management programme, combined with different levels of clinician support, with a control arm (usual treatment); previously reported 3-month findings from the trial included significant improvements in disability, depression, anxiety and pain levels in the intervention arms versus the control arm, with no significant differences among the intervention arms. This analysis showed the early findings persisted, with clinically significant decreases in disability (average reduction ≥27%), depression (≥36%), anxiety (≥38%) and average pain levels (≥21%) in the intervention arms maintained at 12 months and 24 months, with no marked or consistent differences among the three treatment groups.

Comment: These are the 12- and 24-month follow-up data of a previous RCT (79% of n=490) of an internet pain programme (The Pain Course) versus usual wait-list control, showing clinically significant reductions in disability, depression and anxiety were maintained at 12 months and 24 months follow-up. It is interesting that there was no significant difference among the three treatment groups with different levels of clinician support (regular clinician support versus the option of clinician support or no clinician support). I note that the control group data were not assessed, as the control group completed the programme shortly after the initial study. However, it will be interesting to see if the control group was able to further progress in the short and long term. Furthermore, it will be useful to see if there are significant changes in work status and medication use. This study highlights the potential of a cost-effective, accessible and well-designed and delivered internet pain programme to achieve long-term clinical improvements.


Abstract
Non-opioid analgesic modes of pain management are associated with reduced postoperative complications and resource utilisation

Authors: Czoxwicz C et al.

Summary: The impact multimodal analgesia has on opioid use and complications was explored in a retrospective cohort of 181,162 patients with OSA (obstructive sleep apnoea) who had undergone elective lower extremity joint arthroplasty; 88.5% of the patients had received multimodal analgesia (opioids plus ≥1 nonopioid analgesics, including NSAIDs, COX-2 inhibitors, paracetamol (acetaminophen), peripheral nerve blockers, steroids, gabapentin/pregabalin and ketamine) with increasing utilisation trends. Compared with opioid-only analgesia, postoperative outcomes improved in a stepwise manner with increasing analgesic adjectives; patients who received ≥2 additional analgesic modes showed a decrease in prescribed opioid dose of 14.9% and were less likely to experience gastrointestinal complications (odds ratio 0.65 [CI 0.53–0.78]) or require mechanical ventilation (0.23 [0.16–0.32]) or admission to critical care (0.60 [0.48–0.75]).

Comment: Considering peroperative risk factors, OSA has particularly raised concern for respiratory failure, necessitating critical care intervention in the postoperative period. This is a US population-based retrospective cohort study (n=181,182; 2006–2016) of OSA patients undergoing elective lower-limb joint arthroplasty, showing increased use of multimodal analgesia over time (suggesting a dose-response relationship), and associated decreases in opioid prescription, postoperative complications and resource utilisation (especially need for postoperative mechanical ventilation and critical care admission). Interestingly, analysis of individual adjuvants showed that COX-2 inhibitors and NSAIDs were associated with the strongest effect on opioid dose reduction. This is consistent with previous study showing an opioid-sparing effect of multimodal analgesia. Given the retrospective observational nature of the study, causality cannot be established and potential confounders may exist. Overall, this study validates the use of multimodal analgesia in the study population.


Abstract

Opioids for chronic noncancer pain

Authors: Busse JW et al.

Summary: This was a systematic review and meta-analysis of 96 RCTs comparing opioids with nonopioid controls for chronic noncancer pain; 25 trials were conducted in patients with neuropathic pain, 32 in nociceptive pain, 33 in central sensitisation and six in mixed pain types. Compared with placebo, opioid use was associated with a reduction in 10 cm VAS pain score (WMD –0.69 cm [95% CI –0.82 to –0.56]) and an improvement in physical function (2.04 points [1.41 to 2.68]), but more vomiting (5.9% vs. 2.3%). There was low-to-moderate-quality evidence for similar improvements in these pain and physical functioning scores with opioids versus NSAIDs (WMDs –0.60 cm [95% CI –1.54 to 0.34] for pain VAS score and –0.90 points [–2.69 to 0.89] for physical functioning), tricyclic antidepressants (–0.13 cm [–0.99 to 0.74] and –5.31 points [–13.77 to 3.14]) and anticonvulsants (–0.90 cm [–1.65 to –0.14] and 0.45 points [–5.77 to 6.66]).

Comment: This is a systematic review and meta-analysis (96 RCTs; n=26,169; follow-up 1–6 months) of opioid use in neuropathic pain, nociceptive pain and central sensitisation, showing a significant reduction in pain (–0.63 cm on 10 cm VAS) and improved physical function (2.04 of 100-point SF36 physical component score). I note the risk difference for achieving the minimal important difference was 11.9% for pain (1 cm) and for physical function it was 8.5% (10 points). The study also suggested moderate-to-low evidence that opioid use is associated with similar improvements in pain and physical function when compared with NSAIDs, tricyclic antidepressants and synthetic cannabinoids. Interestingly, the study reports no condition-specific differential for neuropathic, nociceptive or central sensitisation conditions, which contrasts with clinical guidelines’ views on headache, fibromyalgia and low back pain. Otherwise this study is consistent with previous reviews and may be useful for psychosocial education regarding the role of opioids in chronic noncancer pain.

Reference: JAMA 2018;320:2448–60

Abstract

Left dorsolateral prefrontal cortex repetitive transcranial magnetic stimulation reduces the development of long-term muscle pain

Authors: Seminovicz DA et al.

Summary: This research randomised 30 healthy individuals to receive five consecutive daily treatments of repetitive TMS (transcranial magnetic stimulation) to the left dorsolateral prefrontal cortex or a sham procedure, starting before the first of repeated intramuscular injections of NGF (nerve growth factor) to induce sustained muscle pain. Compared with the sham procedure, repetitive TMS was associated with significant reductions in muscle soreness, pain intensity and painful area, with a trend for reduced disability; these effects were most evident on the treatment days and lasted for ≤3 days. There was no significant effect of the treatment on depression, anxiety, pain catastrophising or affect, but a trend toward improved cognitive function was seen with repetitive TMS (p=0.007).

Comment: High-frequency repetitive TMS of the left dorsolateral prefrontal cortex is an effective treatment for major depressive disorder, and has shown promise for headache, fibromyalgia and burning mouth syndrome. This is an experimental pain study (n=30) using an NGF-induced muscle pain model in healthy participants, showing 5 days of high frequency (excitatory) left dorsolateral prefrontal cortex repetitive TMS (80 trains of 5-second pulses of 10Hz, and interval of 10 seconds, at 110% resting motor threshold of the first dorsal interosseous muscle) significantly reduced pain intensity and distribution and with a near significant improvement in cognitive task performance. The severity of NGF-induced muscle pain is thought to predict transition from acute to chronic pain. This may have potential for preventing persistent pain after acute nociception. Further study is warranted.

Reference: Pain 2018;159:2486–92

Abstract

1. No submission fees.
3. Categories: Topical Sessions, Free Papers & Posters, Rising Star Award.
ATYPICAL OPIOID
EVERYDAY BENEFITS

• Strong pain relief as effective as oxycodone CR\textsuperscript{1,5,6}
• Significantly less constipation, nausea and vomiting vs. oxycodone CR\textsuperscript{1,5,6}
• Significantly greater improvement in functional outcomes\textsuperscript{†} vs. oxycodone CR\textsuperscript{1,5,6}

*Analgesia not solely derived from opioid agonism. ^S8 analgesic.

#Meta-analysis to assess non-inferior efficacy and tolerability in moderate to severe pain (p<0.001 for all events) in patients with chronic knee osteoarthritis or low back pain. †In Physical and Social Functioning and Role Physical (SF-36 outcomes, p≤0.008).

MINIMUM PRODUCT INFORMATION: PALEXIA\textsuperscript{®} SR (Tapentadol hydrochloride)

INDICATION: Moderate to severe chronic pain unresponsive to non-narcotic analgesics

CONTRAINdications: Known hypersensitivity to tapentadol or any component of PALEXIA SR, in conditions in which mu-opioid receptor agonist activity is contraindicated (e.g., significant respiratory depression and acute or severe bronchial asthma or hypoxia, confirmed or suspected paralytic ileus, severe acid-base or electrolyte disturbances, centrally acting analgesics or psychotomimetic drugs, 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 function; patients with head injury, brain tumors, a history of seizures or any condition that increases risk of seizures, moderate hepatic impairment or biliary tract disease; use in pregnancy (Category C). Should not be used during breastfeeding. Not recommended for children <18 years old. May impair ability to drive or operate machinery. 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 anesthetics, phenothiazines, other tranquilizers, 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 serotoninergic drugs (see full PI).

ADVERSE EFFECTS: Very common (≥5/10): dizziness, somnolence, headache, nausea, constipation (Common ≥7/100 to <1/100): Decreased appetite, anxiety, decreased mood, sleep disorder, nervousness, restlessness, disturbance in attention, tremor, muscle contractions involuntary, flushing, dyspnoea, vomiting, diarrhoea, dyspepsia, pruritus, hyperhidrosis, rash, asthenia, fatigue, feeling of body temperature change, mucosal dryness, oedema. Postmarketing suicidal ideation, angioedema, anaphylaxis and anaphylactic shock.

DOSAGE AND ADMINISTRATION: To be taken orally twice daily with sufficient fluid, approximately every twelve hours, with or without food. Initiation of therapy in patients currently not taking opioid analgesics: start with 50 mg PALEXIA SR twice daily. Initiation of therapy in patients currently taking opioid analgesics: titrate individually to a level that provides adequate analgesia and minimizes side effects under close supervision of prescribing physician; titration regimen in increments of 50 mg twice daily every 3 days shown to be appropriate in most patients in clinical trials. Total daily doses > 500 mg not recommended. Discontinuation of treatment: taper dose gradually to prevent symptoms of withdrawal. Renal impairment: not recommended in severe renal impairment. Hepatic impairment: initiate at 50 mg once daily in moderate hepatic impairment; not recommended in severe hepatic impairment. Elderly patients more likely to have decreased renal and hepatic function - care in dose selection. Not recommended for use in children <18 years old.

Based on approved Product Information dated 27 March 2017.

Before prescribing, please review the Product Information available at www.seqirus.com.au/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.
Betulinic acid, derived from the desert lavender *Hyptis emoryi*, attenuates paclitaxel-, HIV-, and nerve injury-associated peripheral sensory neuropathy via block of N- and T-type calcium channels

Authors: Bellampalli SS et al.

Summary: These authors identified an extract from *Hyptis emoryi* that targets voltage-gated Ca2+ channel activity, with the intent of investigating its use for treating neuropathic pain. The active extract was subjected to bioassay-guided fractionation resulting in three compounds: betulinic acid, oleanolic acid and ursolic acid. They found that betulinic acid was able to inhibit depolarisation-evoked Ca2+ influx in dorsal root ganglion neurons, mainly by targeting low-voltage-gated Ca2+ channels (CaV3, or T-type, and CaV2.2, or N-type). Voltage-clamp electrophysiology experiments showed that betulinic acid exposure resulted in reductions in Ca2+ currents, but not Na+ currents. Betulinic acid was also found to inhibit spontaneous excitatory post synaptic currents and depolarisation-evoked CGRP release from lumbar spinal cord slices, and did not engage human µ, δ or κ opioid receptors. In murine models of chemotherapy-induced peripheral neuropathy, HIV-associated peripheral sensory neuropathy and partial sciatic nerve ligation, intrathecal betulinic acid administration reversed mechanical allodynia without affecting locomotion.

Comment: *Hyptis emoryi* was reported to have analgesic properties and has been used for irritated stomach lining. This mechanistic study showed that betulinic acid inhibits T-type calcium channels (CaV3) and Ca2+ current (KCl-evoked Ca2+ current) in dorsal root ganglion sensory neurons using patch-clamp recording; it also inhibits release of CGRP (using immunomass of lumbar slices). Using experimental models of neuropathic pain (partial sciatic nerve ligation, HIV-induced neuropathy, beta-2−) receptor and an intrathecal catheter) it was shown to reverse mechanical alldynia without motor effect. T-type calcium channels are low-voltage activated calcium channels that conduct small currents that modulate neuronal excitability at the dorsal horn. T-type calcium channels are increased in afferent pain fibres in neuropathic pain states such as traumatic, diabetic and chemotheraphy-induced neuropathy. Given that T-type calcium channels were not linked with opioid signalling pathways (whereas N-type were), betulinic acid has the potential to be a nonopioid therapeutic for chronic pain. Further study is warranted.


Effect of intravenous dexmedetomidine during general anesthesia on acute postoperative pain in adults

Authors: Wang X et al.

Summary: This was a systematic review and meta-analysis of 40 RCTs assessing the analgesic effects of intravenous dexmedetomidine versus saline for acute postoperative pain after surgery in adults who had received general anesthesia. Compared with normal saline, dexmedetomidine was associated with significant decreases in pain intensity 6 hours after surgery and 24 hours after surgery (respective WMDs –0.10 [95% CI –0.19 to –0.01] and –0.21 [95% CI –0.37 to –0.05]), and 0.47 [0.33 to 0.61]), significant reductions in cumulative opioid consumption at 24 hours and in the PACU (–6.76 [–10.16 to –3.35] and –3.11 [–5.20 to –1.03]), reduced rescue analgesic use (relative risk 0.49 [0.33–0.71]) and a longer time to first rescue analgesia (WMD 34.93 [20.27–49.59]).

Comment: Previous studies have suggested an analgesic effect of dexmedetomidine as part of the multimodal analgesia regime. A previous Cochrane review of dexmedetomidine in 2015 concluded very low-quality evidence of dexmedetomidine for acute pain post abdominal surgery due to imprecision, and substantial heterogeneity. This is a meta-analysis of 40 RCTs (sample size range, 30–131) showing dexmedetomidine (0.4–1 µg/kg, 4.0–4.7 µg/kg/h) significantly reduced acute pain (WMD –0.93, on a 10-point VAS at 6 hours) and reduced opioid consumption (–0.76mg, of parenteral morphine equivalents at 24 hours). Despite significant heterogeneity of the studies, this meta-analysis suggests a clinical benefit of dexmedetomidine. Further study is warranted.

Reference: *Clin J Pain* 2018;34:1180–91

Comparison of preoperative administration of pregabalin and duloxetine on cognitive functions and pain management after spinal surgery

Authors: Altiparmak B et al.

Summary: Ninety-four adults from operating rooms and surgical wards and scheduled for elective lumbar disc herniation repair (ASA status I–II) were randomised to receive: i) oral pregabalin 75mg 1 hour before surgery and at postoperative hours 12 and 24; ii) oral duloxetine 60mg 1 hour before surgery and at postoperative hour 24 (with placebo at postoperative hour 12); or iii) placebo at all three timepoints. All three groups showed significant reductions in mean postoperative MoCA (Montreal Cognitive Assessment) scores, with reductions of 1.83, 1.16 and 0.49 points in the pregabalin, duloxetine and placebo groups, respectively. Pregabalin and duloxetine were associated with similar mean VAS scores at all timepoints, and lower scores compared with placebo (p<0.05).

Comment: A recent study showed that duloxetine reduced morphine consumption in the first 48 hours after knee replacement surgery. A previous review on perioperative pregabalin also showed an opioid-sparing effect. This is a randomised, double-blind, placebo-controlled trial (n=94) of elective repair of lumbar herniation patients showing a significant reduction in cognitive function (MoCA) and pain (VAS) scores with pregabalin (75mg at 1 hour preoperatively and at 12 and 24 hours postoperatively) and duloxetine (1 hour preoperatively), compared with a control group. MoCA is a valid and reliable test for patients with mild cognitive impairment and dementia. Given that anaesthesia (e.g. sevoflurane) and surgery already play a role in postoperative cognitive dysfunction, preoperative use of duloxetine may be preferable to pregabalin, especially in elderly patients. Further validation study is warranted.


Escalating opioid dose is associated with mortality: a comparison of patients with and without opioid use disorder

Authors: Hser Y-I et al.

Summary: US prescription drug monitoring programme data were used to explore longitudinal opioid prescribing patterns for 2576 patients with and 5152 controls without OUD over 4 years before death or a comparable period ending in 2014. Individuals with OUD received significantly more opioid prescriptions, a greater number of days of supply and steeper increases of opioid dosages over time than those without OUD. A significant interaction was seen between OUD and mortality for morphine equivalents at both intercept and slope, with the sharpest increase seen in deceased individuals with OUD, who ended with a 20.2g higher level of morphine equivalents prescribed before they died. Factors associated with higher numbers and doses of opioid prescriptions were older age, public health insurance, cancer and chronic pain.

Comment: This is a retrospective population study (n=7728; California Prescription Drug Monitoring Program, 2014) using growth modelling showing that patients with OUD were prescribed higher opioid dosages, which were associated with greater mortality. Furthermore, an escalating prescribing pattern was associated with heightened mortality risk for both OUD patients and controls, more so for OUD patients. Other sources of opioids, prescription or nonprescription, outside the prescription drug monitoring system were not ascertained. I note that the OUD and non-OUD populations had equivalent rates of cancer (13–14%), and a previous study showed cancer deaths account for similar percentages of death among OUD and non-OUD patients; hence, end-of-life care cannot account for the difference between the two groups. Prescribers need to be alert to escalating opioid prescriptions, and sharp escalation of dose/prescription needs to be avoided.


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