Welcome to issue 59 of Pain Management Research Review.

Medication overuse headache, a common type of chronic headache with similarities to substance dependence disorders, is the focus of the first paper selected for this issue, which has investigated the severity of dependence on analgesics and whether it is predictive of successful withdrawal. Other included research has investigated the use of transdiagnostic emotion-focused exposure therapy for patients who have both chronic pain and anxiety or depression. A proof-of-concept study has reported some success with the use of onabotulinumtoxin A for treating pelvic pain in women with endometriosis. This issue concludes with a meta-analysis of RCT data on the efficacy of duloxetine for acute postoperative pain.

Please remember, your comments and feedback are always welcome.

Kind Regards,
Dr Tim Ho
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Severity of analgesic dependence and medication-overuse headache

Authors: Lundqvist C et al.

Summary: Analgesia dependence was compared for 60 patients with medication overuse headache, 15 patients with chronic headache without medication overuse and 25 population controls. Among the patients with medication overuse headache, 62% were found to overuse simple analgesics, including 38% who used centrally acting analgesics, with half being classified as DSM-IV substance-dependent. Greater proportions of dependence were seen in patients who used centrally active medications and those with high SDS (Severity of Dependence Scale) scores. A ROC analysis revealed that SDS scores accurately identified dependence (area under the curve, 88%). Analgesia withdrawal was more successful in patients with lower SDS scores (p=0.004).

Comment: Medication overuse headache is characterised by overuse of analgesics (≥15 days a month for simple analgesics or ≥10 days a month for triptans or opioids), and is associated with worsening of a pre-existing headache disorder. There are many clinical similarities between medication overuse headache and substance-use disorder. This is a prospective cohort study (n=100) showing that medication overuse headache patients fulfilled the DSM-IV criteria for substance-dependence, even though the majority used simple analgesics. SDS score was shown to accurately identify dependence using ROC analysis. The SDS has been shown to have good psychometric properties. Whether medication overuse headache patients are ‘dependent’ or ‘dependent-like’ is controversial, but dependence should not be excluded. The lower SDS score in medication overuse headache patients is associated with more successful outpatient withdrawal. This may have treatment implications. It will be interesting to look at stratified treatment based on SDS score in future studies.


Prescribing of opioids and benzodiazepines among patients with history of overdose

Authors: Griggs C et al., the PRIMUM Group

Summary: Prescribing of opioids and benzodiazepines was reported for a retrospective cohort of patients who had presented with an opioid or benzodiazepine overdose to a large healthcare system. Among 60,129 prescribing encounters for opioids and/or benzodiazepines, 543 involved patients with a prior opioid or benzodiazepine overdose, and within this cohort of 404 unique patients, 97 had made >1 visit that involved a prescription opioid and/or benzodiazepine. Just over half the prescriptions (54.1%) were to patients who had an overdose within 2 years of the documented prescribing encounter. Half the encounters (49.9%) were related to prescriptions in the outpatient clinical setting and 31.5% were in the emergency department setting. Having a previous overdose, whether intentional or unintentional, is a high-risk case for further opioid prescribing. The combination of a benzodiazepine with an opioid is also known to be a significant risk factor for overdose death. This is a retrospective chart review showing 404 episodes of high-risk prescribing (n=60,129) of an opioid or benzodiazepine, in a 1-month period in 2015, for patients who had a previous presentation for overdose using insurance claims data. Most of the prescribing occurred in the outpatient setting, and it is not clear if the prescribers were aware of the previous overdose. The incorporation of these data into future real-time monitoring systems may be useful to support clinical decision making. More investment is needed in multidisciplinary pain management for this patient cohort.

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Conventional-SCS vs. burst-SCS and the behavioral effect on mechanical hypersensitivity in a rat model of chronic neuropathic pain: effect of amplitude

Authors: Meuwissen KPV et al.

Summary: Relationships between amplitude (charge per second) and behavioural effects for both conventional and biphasic burst SCS (spinal cord stimulation) were explored in a rat model of chronic neuropathic pain. Twelve rats underwent unilateral partial sciatic nerve ligation and implantation with quadripolar electrodes in the epidural space at T13 in this research. Paw withdrawal thresholds to von Frey monofilaments across a range of SCS intensities were used to assess mechanical hypersensitivity at multiple timepoints during 60 minutes of stimulation and at 30 minutes post-stimulation. The efficacy of conventional SCS improved as amplitude increased, whereas a nonmonotonic relationship was seen between the efficacy of burst SCS and amplitude. Conventional SCS at 66% motor threshold and burst SCS at 50% motor threshold were equally effective for normalising mechanical hypersensitivity, but during the assessed time period, burst SCS required a significantly greater mean charge per second. Conventional SCS resulted in a better behavioural outcome than burst SCS when applied at comparable mean charges per second.

Comment: Burst firing results in a calcium wave on which sodium spikes crest at the spinal/thalamic level, causing a super-actional potential that overrides tonic activity at the cortex level. Burst SCS was thought to prolong pulsed width to polarise dendrites and axon terminals and alter synaptic transmission. This is an animal study (n=12) of T13 epidural SCS leads using a sciatic nerve ligation model, showing that paw withdrawal threshold improvement correlates with increased amplitude with conventional SCS, but not with burst SCS. Burst SCS was shown to require a greater mean charge per second to achieve the same improvement in mechanical hypersensitivity. Interestingly, conventional SCS at 66% motor threshold and burst SCS at 50% produced equal efficacy in improving mechanical hypersensitivity. It will be interesting to look at actual Burst-DR™ stimulation, supraspinal effects and measurement of overstimulation.

Reference: Neuro modulation 2018;21:19–30

Individualization of migraine prevention: a randomized controlled trial of psychophysically-based prediction of duloxetine efficacy

Authors: Kaiser LB et al.

Summary: Patients who experience migraines were randomised to receive duloxetine (n=27) or placebo (n=28), and psychophysical pain measures were used to predict efficacy for migraine prevention. Compared with placebo, duloxetine was associated with greater participant estimation of migraine improvement (52.3% vs. 26.0% [p=0.012]) with higher pretreatment pain ratings for tonic heat pain (p=0.012). Greater pain sensitivity at baseline was a significant predictor of greater migraine improvement among duloxetine recipients (r=-0.47 [p=0.013]) but not among placebo recipients (r=-0.36 [p=0.060]).

Comment: Previous preclinical studies of SNRTs (serotonin-norepinephrine [norepinephrine] norepinephrine] reuptake inhibitors) would help restoration of diffuse noxious inhibitory control/conditioned pain modulation, and gabapentinoids would reduce temporal summation. This is an RCT (n=55) showing predictors of response to duloxetine (in migraine prevention), including greater tonic heat pain and greater pain sensitivity, using psychophysical testing. Mechanical temporal summation, offset analgesia, tonic heat pain, conditioned pain modulation, anxiety/depression and catastrophisation were measured. This study is interesting, as a model of non-ongoing pain was used. This study suggests that improvement was predicted by pronociceptivity (with higher pain rating with suprathreshold noxious heat). Interestingly, this relationship was not directly observed with conditioned pain modulation or offset analgesia alone. It will be interesting to look at the correlation using multiple regression analysis using both independent variables of pronociceptivity and conditioned pain modulation/offset analgesia.


Efficacy of a transdiagnostic emotion-focused exposure treatment for chronic pain patients with comorbid anxiety and depression

Authors: Boersma K et al.

Summary: Adults with chronic musculoskeletal pain and functional and emotional problems were randomised to 10–16 sessions of transdiagnostic emotion-focused exposure (‘hybrid’) therapy that integrates exposure in vivo for chronic pain based on the fear-avoidance model with an emotion-regulation approach informed by procedures in dialectical behaviour therapy (n=58) or eight modules of CBT-based internet-delivered pain management addressing topics like pain education, coping strategies, relaxation, problem solving, stress and sleep management (active control; n=57) in this open-label trial. Overall, 78% and 81% of the participants completed post-treatment and follow-up assessments, respectively. Compared with the control group, the hybrid treatment group exhibited significantly better post-treatment outcomes for pain catastrophising and pain interference, and significantly better follow-up outcomes for depression and pain interference. There was no significant between-group difference for anxiety or pain intensity.

Comment: A previous meta-analysis suggested emotional distress and cognitive behavioural risk factor predicts poor outcome in chronic pain patients. This is an RCT (n=115) comparing hybrid emotion-focused treatment and internet-delivered CBT, showing clinically significant improvements in both groups, favouring the hybrid group (non-significant). Interestingly, patients self-selected into this study, which may limit generalisability. The transdiagnostic approach is based on the idea that chronic pain and emotional problems share certain cognitive and behavioural processes, and treatment of these processes can facilitate improvement in patients with comorbid chronic pain and high levels of emotional problems. The hybrid treatment focuses on the exposure for pain and emotion-related avoidance behaviour, with the integration of dialectical behaviour therapy skills, such as emotional regulation, acceptance and desired goal pursuit. Further study is warranted.

Reference: Pain 2019;160:1708–18

Abstract

Brief cognitive behavioral therapy for chronic pain

Authors: Beehler GP et al.

Summary: Preliminary effectiveness data were reported for 118 patients with chronic pain who received the Brief CBT-CP (Brief Cognitive Behavioral Therapy for Chronic Pain), an abbreviated, modular treatment designed for use in primary care. The patients had experienced significant improvements for a composite of pain intensity and functional limitations by their third appointment, with an improvement also seen for pain-related self-efficacy outcomes, albeit with a smaller effect size. An exploratory analysis suggested that the most significant gains were seen for the modules addressing psychoeducation and goal setting, pacing and relaxation training.

Comment: This is a pragmatic cohort study (n=180) showing improvement in pain severity, pain-related Interferences and pain-related self-efficacy using brief CBT for chronic pain delivered in a primary care behavioral health setting. These were six 30-minute appointments to deliver a brief pain management programme. I note that this is not an RCT. The participation varied significantly in the study, with many attending only 2–3 appointments. However, given the brevity and setting, this approach has potential scalability. Further study is warranted.


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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- Significantly greater improvement in functional outcomes† vs. oxycodone CR1,5,6

*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® 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; 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 any hypnotics, centrally acting analgesics or psychotropic 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 or patients with head injury, brain tumors, a history of seizures or any condition that increases risk of seizures, moderate hepatic impairment of biliary tract disease; Including acute pancreatitis, 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 analogues, general anaesthetics, phenothiazines, other tranquillisers, 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 (≥20%): Dizziness, somnolence, headache, naussea, constipation. Common (5% to <10%): Decreased appetite, anxiety, depressed mood, sleep disorders, nervousness, dizziness, disturbance in attention, tremor, muscle contractions involuntary, flushing, dyspnea, vomiting, diarrhea, dyspepsia, pruritus, dysuria, rash, chest pain, 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 liquid; approximately every twelve hours, with or without food. Initiation of therapy in patients currently not taking similar analgesics: start with 50 mg PALEXIA SR twice daily; titration of therapy in patients currently taking opioid analogues: start with 50 mg twice daily and increase 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. REFERENCES: 1. PALEXIA SR Approved Product Information. 2. Raffa RB. Pain Management Research Review. 3. SAA Journal of Pain and Palliative Care Pharmacotherapy. 4. Seqirus Australia Pty Ltd. 5. Lumpa A et al. Drug Information Journal. 6. Bowler J. Drug Intelligence. 7. Raffa RB. NEMA Research Group, Naples, Florida, USA 2017.

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Botulinum toxin for chronic pelvic pain in women with endometriosis

**Authors:** Tandon HK et al.

**Summary:** Thirty-nine women with endometriosis received topical anaesthesia and onabotulinumtoxin A 100U injected transvaginally into pelvic floor muscle spasm areas under EMG guidance in this proof-of-concept cohort study with follow-up of ≥4 months. Before injection, 11 of the 13 women had spasm in >4 of the 6 pelvic muscles assessed with a median VAS score of 5, and at 4–8 weeks post-treatment, spasms were absent or involved ≤3 muscles (p<0.0005) with a median VAS score of 2 (p<0.0001). In addition, seven of the women required less pain medication, and disability decreased in six of the eight women with moderate or greater disability at baseline (p=0.0033). Among women followed for 1 year (n=11), seven reported that the effects of treatment lasted 5–11 months. Only mild and transient adverse events were recorded.

**Comment:** Conventional treatment for endometriosis involves surgery to remove lesions and hormonal therapy to suppress lesion growth. This is a prospective case series (n=13) of BOTOX® injections in endometriosis patients with pelvic pain and pelvic floor spasms, refractory to hormonal and surgical treatment, showing a significant reduction in pain and spasm and a reduction in pain medication at 1 year. One hundred units of onabotulinumtoxin A was divided among 3–4 areas of muscle spasm, using an EMG needle, including obturator internus, lateral to uterine cervix, iliococcygeus/lateral vaginal wall and pubococcygeus. The patients did not have urinary retention or incontinence. Botulinum toxin was thought to affect nociception via peripheral and central pain pathways. Further validation study is warranted.

**Reference:** Reg Anesth Pain Med 2019;44:886–92

Remote electrical neuromodulation (REN) in the acute treatment of migraine

**Authors:** Rapoport AM et al.

**Summary:** This was a post hoc analysis of data from a recent study reporting pain relief and few adverse events associated with REN (remote electrical neuromodulation); this analysis focussed on acute care of 99 participants with migraine comparing this treatment with usual care (participant preference). Compared with usual care, greater proportions of the REN group reported pain relief at 2 hours post-treatment (66.7% vs. 52.5% [p<0.05]) and pain relief at 2 hours in >1 of two attacks (84.4% vs. 68.9% [p<0.05]), but with no significant difference in the proportion who were pain-free at 2 hours.

**Comment:** This is a post hoc analysis of a double-blind RCT (n=99) of REN in the acute treatment of migraine showing noninferiority at 2 hours when compared with current acute migraine therapies. The REN device provides 45 minutes of biphasic square pulses of 100–120Hz, 400 µsec and up to 40mA suprasensory threshold/subpain threshold stimulation. The stimulation is applied to the lateral upper arm between the lateral deltoid and triceps. Usual care included triptans, simple analgesia and nonpharmacological treatment. REN is thought to induce conditioned pain modulation to modulate pain in remote body regions. Further translational study is warranted.

**Reference:** J Headache Pain 2019;20:83

The outcome of pulsed radiofrequency treatment according to electrodiagnosis in patients with intractable lumbar sacral radicular pain

**Authors:** Park CH & Lee SH

**Summary:** Outcomes following pulsed radiofrequency according to electrodiagnosis results were reported for patients with chronic intractable lumbar sacral radicular pain related to failed back surgery syndrome. The patients were classified according to the electrodiagnostic result (no definite finding [n=28], radiculopathy [n=31] or neuropathy [n=23]). Patients with neuropathy had less pain relief after treatment compared with those with radiculopathy and those with no definite findings, with a lower proportion achieving pain reduction of ≥50%. No significant differences were seen among the groups for disability.

**Comment:** Epidural steroid injection was thought to suppress inflammatory cytokines and chemokines and block transmission of nociceptive C fibres. Pulsed radiofrequency was thought to produce a nondestructive electromagnetic field that changes behavioural and molecular hypersensitivity of nerves through suppression of proinflammatory genes, such as TGF (tumour necrosis factor-α) and interleukin-6, and upregulates expression of hyperpolarisation activated cyclic nucleotide-gated channels (HCN) in the dorsal root ganglion. A previous study suggested responder rates of ~70% and 22.9% for cervical and lumbar radicular pain, respectively, at 6–12 months. This is a prospective cohort study (n=82) showing the responder rate was lower in patients with an EMG/nerve conduction study diagnosis of neuropathy, as compared with radiculopathy or nonspecific findings. Pulsed radiofrequency treatment was given at 42°C, with 20 msec/2Hz current for 4 minutes. Further dose-response study is still needed.

**Reference:** Pain Med 2019;20:1697–701

Perioperative dextroamphetamine for acute postoperative analgesia

**Authors:** Zorrilla-Vaca A et al.

**Summary:** This was a meta-analysis of nine RCTs comparing dextroamphetamine (n=285) with placebo (n=289) for acute postoperative pain. Compared with placebo, dextroamphetamine significantly reduced: i) pain scores at 4 and 24 hours postoperatively (respectively mean differences, –0.9 [95% CI –1.33 to –0.47] and –0.94 [–1.56 to –0.33]); ii) opioid use at 24 hours and 48 hours (respectively standardised mean differences, –2.24 [–4.28 to –0.19] and –2.21 [–4.13 to –0.28]); and iii) PONV (risk ratio 0.69 [95% CI 0.49–0.95]). No significant between-group differences were seen for side effects.

**Comment:** Postoperative pain is complex and involves multiple mechanisms, such as surgical wound, inflammation, sensitisation of somatic/visceral nerves and reduction in the inhibitory pathway at the spinal cord and brainstem. This is a meta-analysis of nine RCTs (n=574) of patients in the acute perioperative period showing a significant reduction of pain at 4–48 hours in the dextroamphetamine group. There were associated reductions in opioid use and PONV. The dose (30–60mg), timing (30 minutes to 2 days before surgery) and duration (24 hours to 6 weeks) of dextroamphetamine varied between studies. The reduction in opioid consumption did not achieve clinical importance (10mg intravenous morphine equivalents). Further translational study is warranted.

**Reference:** Reg Anesth Pain Med 2019;44:959–65

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