Welcome to issue 46 of Pain Management Research Review.

To begin this issue, a cost analysis of SCS (spinal cord stimulation) for failed back syndrome found that while the initial cost is high, the benefits over time support the long-term cost utility of this treatment. Research from the US found that it is not uncommon for drug counsellors to have perceived barriers to treating patients with chronic noncancer pain. Authors from Ireland have conducted a thorough review of the importance of empathy when managing pain patients. Another review article concludes this issue with an interesting discussion on how the discovery of the endogenous opioid system has impacted on how physicians understand and manage pain in their patients.

I hope you find these and the other selected research papers helpful in your everyday practice. Please don’t hesitate to send in your comments and suggestions.

Kind Regards,
Dr Tim Ho
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Long-term cost utility of spinal cord stimulation in patients with failed back surgery syndrome

Authors: Harrison Farber S et al.

Summary: This retrospective study compared healthcare utilisation associated with SCS (n=5328) versus conventional management (n=117,499) in patients with failed back surgery syndrome. Compared with conventional management, SCS system implantation was associated with greater total costs at the time of implantation (cost ratio 1.74 [95% CI 1.41–2.15]), but costs decreased significantly and sustainably by 68% in the year after SCS implantation (0.32 [0.24–0.42]), and continued to decrease by an average of 40% each year over follow-up analyses at 1, 3, 6 and 9 years after SCS implantation (0.60 [0.55–0.65]).

Comment: This is a retrospective cost utility regression modelling using the ICD-9 codes from Truven Reuters MarketScan database, showing significant cost savings at 1, 3, 6 and 9 years after SCS implantation (2010–2012); specifically, the annualised cost was more than halved in the SCS group. The cost associated with reoperation after implantation was also captured. A previous UK study showed cost neutrality at 5 years, with 65% of the SCS patients discontinuing pain-related drugs. It will be interesting to see if the data can be reproduced locally in Australia. Furthermore, I wonder whether the reported cost savings translate into improvements in patients’ functional outcomes.

Abstract

Efficacy of cannabis-based medicines for pain management

Authors: Aviram J & Samuely-Leichtag G

Summary: This was a systematic review of 43 RCTs (n=2437) comparing the analgesic effects of cannabis-based medicines with placebo; 24 of the RCTs (n=1334) were included in a meta-analysis. There was limited evidence that compared with placebo, cannabis-based medicines provided greater pain reductions in chronic pain (p<0.0001), especially when administered by inhalation (p=0.001). While some of the trials included in the review reported clinically significant decreases in pain scores of ≥2 points, 30% or ≥50%, such effects were not apparent in most of the RCTs. As such, the authors concluded that while favourable results were seen for cannabis-based medicines over placebo in the primary analysis, the clinical significance is uncertain. CNS and GI adverse events were the most prominent.

Comment: This is a meta-analysis of 24 eligible RCTs (1334 patients), concluding limited evidence of efficacy, with a small effect size, primarily for neuropathic pain, with inhaled cannabinoids being the more studied route of administration. Notably, some but not the majority of the studies showed clinically significant improvements. Furthermore, there was a considerable incidence of adverse events, with high rates of CNS-related adverse events such as dizziness, drowsiness and cannabinoid-related vision impairment, which would have significant implications for driving, work and function. Better powered studies with larger sample sizes, homogenous indications and different cannabis forms are warranted.

Abstract
**Opioid prescription levels and postoperative outcomes in orthopedic surgery**

**Authors:** Cozowicz C et al.

**Summary:** The relationship between degree of opioid use and risk for postoperative complications was explored for 1,035,578 lower joint arthroplasty procedures and 2,209,933 spinal fusion procedures performed in the US over an 8-year period. Compared with the lowest quartile of opioid dosing, opioid dosing in the highest quartile was associated with significantly increased likelihoods of deep vein thrombosis, postoperative infections, urinary complications and respiratory complications, and significantly increased length of stay and costs (p<0.001 for all). Higher opioid dosing significantly decreased the likelihood of cerebrovascular complications (p=0.004) and had no impact on the likelihood of myocardial infarction. There were generally more opioid prescriptions for patients undergoing spinal procedures, with stronger effects seen for increased length of stay, costs and GI and urinary complications.

**Comment:** This is a retrospective, observational study, using multilevel multivariable logistic regression models of data from the US Premier Perspective database 2006–2013, showing higher opioid prescription was associated with increased postoperative complications, especially thromboembolic, infectious and GI, after elective primary total joint arthroplasty or spinal fusion. Notably, the upper quartile of opioid use for the day of surgery and the day thereafter was defined as >550mg oral morphine equivalents per day for spinal fusion surgery, and >765mg/day for primary total hip or knee arthroplasty. The findings are consistent with current mechanistic evidence; previous experimental research has shown that morphine antagonises prostaglandin E1-mediated inhibition of platelet aggregation, and also suppresses humoral and cell-mediated immunity. High-dose opioids may also delay postoperative mobilisation. Despite the data not allowing any conclusion regarding causality, they do allow a basis for further clinical trials.

**Reference:** Pain 2017;158(12):2422–30

**Abstract**

**Analgesia nociception index for the assessment of pain in critically ill patients**

**Authors:** Chanques G et al.

**Summary:** This diagnostic accuracy study measured the validity and performance of the ANI (Analgesia Nociception Index), a 100-point electrophysiological monitoring tool based on spectral analysis of heart rate variability; a score of zero denotes minimal parasympathetic tone and maximal stress-response and pain. The researchers continuously recorded mean ANI and instant ANI scores for each patient before, during and after routine care procedures such as turning, tracheal suction and dressing change, in noncomatose, noncommunicative ICU patients. There may be an advantage of ANI in patients receiving neuromuscular blocking agents (as compared with behavioural pain tools). However, it is difficult to account for factors such as vasopressors and mechanical ventilation. Further study using an RCT design will be warranted to measure the impact of ANI.

**Comment:** This is a cross-sectional study of 33 patients ≥6 months after cooled RFA for OA of the knee showing a 35% success rate in a combined outcome. Categorical data including a >50% reduction in NRS score, reduction of >3.4 in MOSIII and PGIC score of ‘very much improved’ were used. Notably, the mean body mass index was 31.0 kg/m² and more than half of the patients had a bilateral procedure. It will be interesting to see if patients are able to further progress with a pain management programme in a prospective study. Further investigation using functional outcome measures, such as WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index), PCS (Pain Catastrophizing Scale) and DASS (Depression Anxiety Stress Scales), is warranted.

**Reference:** Pain Med 2017;18(9):1631–41

**Abstract**

**Drug counselor responses to patients’ pain reports: a qualitative investigation of barriers and facilitators to treating patients with chronic pain in methadone maintenance treatment**

**Authors:** Beitel M et al.

**Summary:** These researchers interviewed 30 drug counsellors with no prior training in pain management to ascertain how they respond to the clients who report chronic pain during methadone maintenance sessions. The interviewees’ responses identified the following counsellor factors that act as barriers: i) lack of expertise in managing co-occurring chronic pain and opioid use disorder; ii) complexities associated with patients’ treatment requirements; iii) medication regimen concerns; iv) reliance on patient self-reporting; and v) lack of patient improvement. Facilitators identified were empathy, attending to small changes and self-reflection. The counsellors’ perceptions of patient-related barriers included prior negative interactions with health providers, attenuated social roles, decreased motivation and negative attitudes regarding opioid-use disorder. There were also logistical barriers identified, including unsatisfactory pain management referrals, limited time with the counsellor and reduced treatment adherence; consulting with medical providers was identified as a logistical facilitator.

**Comment:** This is a qualitative cross-sectional study, using interview data from 30 drug counsellors in methadone maintenance treatment, identifying key barriers or facilitators in the treatment of patients with chronic pain in methadone maintenance treatment. Methadone maintenance treatment patients with chronic pain are a vulnerable population, with risk of stigma complicating providers’ decision making. Notably, there is a need for more expertise in managing chronic pain and improved understanding of biopsychosocial models of chronic pain among counsellors (rather than defaulting to a medical paradigm). Further evaluation on clinical training and supervision in an integrated treatment model for counsellors is warranted.


**Abstract**
CONFIDENCE
IN PAIN RELIEF*

*PALEXIA SR has proven efficacy and GI tolerability
profile in patients with moderate to severe osteoarthritis,
chronic low back pain, diabetic peripheral neuropathy
and cancer pain

PALEXIA® SR
Tapentadol Sustained Release

PBInformation: Restricted benefit. Chronic severe disabilising 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.

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

MINIMUMPRODUCT 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 alcohol, 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 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. Not recommended for children <16 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 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 (≥1/10): dizziness, somnolence, headache, nausea, constipation; Common (≥1/100 to <1/10): Decreased appetite, anxiety, depressed mood, somnolence, sleep disorder, nervousness, restlessness, disturbance in attention, tremor, muscle contractions involuntary, flushing, dyspnoea, vomiting, diarrhoea, dyspepsia, pruritus, hyperhidrosis, rash, asthma, 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, whole with sufficient liquid, 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: nature, administration and mean daily dose of previous medication should be taken into account. Titration and maintenance: titrate individually to a level that provides adequate analgesia and minimises side effects under close supervision of prescribing physician; titration regimen in increments of 50 mg PALEXIA SR twice daily. Initiation of therapy in patients currently taking opioid analgesics: nature, administration and mean daily dose of previous medication should be taken into account. Titration and maintenance: titrate individually to a level that provides adequate analgesia and minimises side effects under close supervision of prescribing physician; titration regimen in increments of 50 mg PALEXIA SR twice daily. REFERENCES: 1. PALEXIA SR Approved Product Information, 27 March 2017. PALEXIA® SR is a registered trademark of Grünenthal Pty Ltd. PALEXIA® SR is distributed by Seqirus (Australia) Pty Ltd under licence from Grünenthal Pty Ltd. Seqirus (Australia) Pty Ltd ABN 66 120 398 067, 63 Poplar Road Parkville, Victoria 3052, www.seqirus.com.au. Medical Information: 1800 642 865. Seqirus™ is a trademark of Seqirus UK Limited or its affiliates. Date of preparation: October 2017. SEQIPALX08170346b. 14343 RR.
The safety profile of parecoxib for the treatment of postoperative pain

Authors: Schug SA et al.

Summary: Pooled data from 28 randomised, double-blind, placebo-controlled clinical trials and 10 years of postauthorisation data were analysed to investigate the CV, renal and GI safety of parecoxib. The clinical trial data analysis showed that event rates were largely similar for the respective pooled parecoxib versus placebo arms: 1.0% vs. 0.9% for renal failure and impairment, 0.3% vs. 0.2% and 0.2% vs. 0.1% for arterial and venous CV embolic/thrombotic events, respectively, 8.7% vs. 8.6% for hypersensitivity/anaaphylactic reactions, 2.6% vs. 2.1% for hypotension, 2.5% vs. 2.8% for angio-oedema. In the postauthorisation data analysis of 69,567,300 units of parecoxib, there were 35 reports of GI ulceration-related events (all serious), 77 of renal failure or impairment (68 serious), 66 of CV embolic or thrombotic events (64 serious), 32 of hypersensitivity reactions including hypotension-related events (25 serious), 17 of severe cutaneous adverse events (all serious) and 18 of masking signs of inflammation (all serious); most reported outcomes were classified as recovered or recovering.

Comment: COX (cyclo-oxygenase)-2 inhibitors have been developed to reduce some side effects such as GI ulceration and bleeding compared with conventional nonsteroidal anti-inflammatory drugs. This is a pooled analysis of 28 RCTs and postmarketing data of parecoxib showing a low GI-related event rate of 0.2%, and other adverse events such as renal impairment and CV embolic and thrombotic events. A previous head-to-head study also showed lower GI adverse events with parecoxib compared with intravenous ketorolac. It will be interesting to look at the correlation between risk factors for GI events (e.g. elderly, concomitant aspirin/corticosteroids/anticoagulants, active GI disease) and parecoxib.

Abstract

Exploring the facets of empathy and pain in clinical practice

Authors: Roche J & Harmon D

Summary: The authors of this literature review explored the role of empathy in pain medicine practice. They identified the following four major themes: i) the neural basis for empathy and pain; ii) the value and challenges of practicing empathy pain medicine; iii) stigma and empathy for pain; and iv) empathy and physician education and training. They concluded that there is a deserved, unchallenged place for empathy in medical care, especially in pain medicine and medical education, and highlighted the importance of nurturing empathy at all levels of professional expertise.

Comment: This is a review of literature on empathy and pain that identified themes of value, stigma and physician training. The hallmark of neural basis was the discovery of mirror neurons in macaque monkeys in the 1990s, where the premotor cortex fired when the monkey saw mirror actions performed by another monkey. As part of pain communication, empathy can elicit prosocial behaviour toward a person in pain. Medical expertise can physicians to downregulate their own emotional distress. Furthermore, stigma can cause ego depletion and negatively impact on empathy. Banja has proposed ways to prevent ego depletion, such as the development of humility and acceptance of the limitations of medicine.

Reference: Pain Pract 2017;17(8):1089–96
Abstract

Lumbopelvic core stabilization exercise and pain modulation among individuals with chronic nonspecific low back pain

Authors: Paungmali A et al.

Summary: Seven male and 18 female patients with chronic nonspecific LBP underwent the following three experimental interventions in a randomised crossover manner with 48 hours between interventions: i) lumbopelvic stabilisation training; ii) a passive automated cycling intervention; and iii) a control intervention. Compared with the passive automated cycling and control interventions, lumbopelvic stabilisation training was associated with significantly improved pressure pain threshold (p<0.01) and pain intensity (p<0.001), and the heat pain threshold was significantly improved compared with the control intervention (p<0.05); there were no significant effects on the cold pain threshold.

Comment: This is a crossover RCT comparing lumbopelvic stabilisation training, passive cycling and a control intervention in patients with chronic nonspecific LBP. Showing improvements in pressure pain threshold, heat pain threshold and pain intensity. Lumbopelvic core stabilisation exercises were performed in a supine position with hips and knees in flexion, with pressure biofeedback at 40mm Hg at L2, and using an abdominal hollowing manoeuvre and leg/arm movement. Improved motor control mechanisms may reduce peripheral nociceptive drive and hence pain threshold. Previous study has shown improved core motor control can reduce shear force to the lumbar spine. The study looked at the immediate effects of lumbopelvic stabilisation training. Further study looking at long-term effects is warranted.

Reference: Pain Pract 2017;17(8):1088–14
Abstract

Discovery of endogenous opioid systems: what it has meant for the clinician’s understanding of pain and its treatment

Authors: Ballantyne JC & Sullivan MD

Summary: These authors talked about how the discovery of the endogenous opioid system has affected how pain is managed clinically. Their paper included discussion on the neurobiological basis of addiction and of pain, how pain affects behaviours, the role of the endogenous opioid system in socialisation, chronicification of pain, and the role of stress. They also address the question of opioid use for treating chronic pain.

Comment: The endogenous opioid system is a common pathway between dysfunctional reward centres in addiction and pain pathways in chronic pain. Previous study has shown shared processing of pain and reward, such as opposing motivator reward and behavioural drive. Dunbar postulates that human social bonding is also dependent on endogenous opioids (BOSTA). When exogenous opioids are used chronically, normal motivational behaviours and coping may be hijacked and sacrificed, which may potentially impact family and community.

Reference: Pain 2017;158(12):2290-300
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.