A new hypothesis for CRPS (complex regional pain syndrome), which makes for interesting reading. US research has looked at barriers to providing nonpharmacological therapy for chronic pain, as well as those for reducing opioid use. An RCT has reported that both anxiety and pain can be reduced by the use of melatonin or gabapentin in patients undergoing lumbar surgery. Your input is always valued, so please don’t hesitate to send in your feedback and suggestions.

Kind Regards,
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Treatment of chronic pain with various buprenorphine formulations

Authors: Aiyer R et al.

Summary: This systematic review of 25 RCTs reported on the efficacy of five buprenorphine formulations versus opioid analgesics or placebo for the treatment of chronic pain. Buprenorphine was associated with clinically significant benefits for chronic pain versus comparators in 14 of the studies, including one of six that investigated sublingual and intravenous buprenorphine, two of three that investigated buccal buprenorphine, 10 of 15 that investigated transdermal buprenorphine and the only study that investigated sublingual buprenorphine combined with naloxone. None of the included studies reported any serious adverse events.

Comment: Buprenorphine, a partial µ-agonist and κ-antagonist, is thought to have advantages in chronic pain patients with substance-use disorder, or opioid-induced hyperalgesia. This is a systematic review of 25 heterogeneous RCTs suggesting transdermal buprenorphine is effective analgesia in chronic pain, and a trend for efficacy for buccal buprenorphine was seen in a limited number of studies. The studies were mostly short duration, and there was significant heterogeneity in the outcome measures and study populations. It is worth noting that Neumann’s study showed daily-dose sublingual buprenorphine/naloxone was comparable with oral methadone (3–4 times per day) for pain reduction in chronic nonmalignant back pain. Also, Mittra’s study showed transdermal buprenorphine was not inferior to transdermal fentanyl. Further study in chronic pain patients with active or historical substance-use disorder and opioid-induced hyperalgesia is warranted.

Abstract

A new hypothesis for the pathophysiology of complex regional pain syndrome

Authors: Russo M et al.

Summary: These authors presented a new overarching hypothesis to explain CRPS invoking four dynamically changing and interacting components of tissue trauma, pathological pain processing, peripheral and central autonomic dysfunction and immune dysfunction, primarily involving excessive and pathological dendritic cell activation after atrophy or trauma. They outline pathophysiological changes that may cause CRPS via a cascade of events that involve dendritic cells and the cholinergic anti-inflammatory pathway, as well as changes that allow CRPS to persist into its chronic phase.

Comment: This is a medical hypothesis to explain the cause of CRPS through a common pathway via dendritic cell activation, leading to endothelial dysfunction, microglial activation, dorsal root ganglia sensitisation, immune activation and basal ganglia dysfunction. Dendritic cells are a class of antigen-presenting cells for immuno-surveillance and host response co-ordination. Uprogation of dendritic cell activity may cause exaggerated downstream effects, hence the multiple phenotypical changes. Kingery et al. have developed a rat tibia fracture model of CRPS, which will be useful for future studies. Further research into inhibition of dendritic cell activation, maturation and migration may be promising. We know that oral corticosteroids and zoledronic acid have been used for CRPS in its earlier phase, and these are known to inhibit dendritic cells. Vagus nerve stimulation and the selective cholinergic agonist a7nACHR are known to inhibit dendritic cells. Vagus nerve stimulation and the cholinergic anti-inflammatory pathway may be explored to regulate dendritic cell activity. I look forward to further studies on dendritic cells and CRPS.

Reference: Medical Hypotheses 2018;119:41–53
Abstract
Chronic pain after traumatic brain injury: pathophysiology and pain mechanisms

Authors: Irvine K-A & Clark JD

Summary: These authors reviewed published literature on the pathophysiological changes resulting from TBI (traumatic brain injury), and how these may be involved in the development of postinjury pain persistence. They identified evidence that while pain is common following TBI, many potential mechanisms could explain it, including neuroinflammation, excitotoxicity and axonal degeneration, and it is not clear how each of these contributes at an individual patient level. They also highlighted priority areas for research that may help design and develop therapies for both pain reduction and improving overall outcomes.

Comment: A previous review of 42,000 TBI patients showed 54% experience chronic pain. However, there is a poverty of information regarding mechanisms. This review looked at evidence on neuroinflammation, excitotoxicity and axonal degeneration. Notably, acute increases in extracellular glutamate levels have been shown in experimental brain trauma models, through astrocytic glutamate transporters. In animal models of TBI, neuroinflammation was demonstrated in pain centres, with release of cytokines (tumour necrosis factor-a and interleukin-1β), chemokines (e.g. CX3CR1 and BDNF brain-derived neurotrophic factor) promoting neuroplasticity. A previous functional MRI study by Jang et al. showed that the degree of diminished anisotropy in the periaqueductal grey (i.e. degree of axonal degeneration) correlates with pain severity. Further study is warranted to advance the understanding of pain mechanisms in TBI and targeted treatments.


Abstract

Barriers to using nonpharmacologic approaches and reducing opioid use in primary care

Authors: Giannitrapani KF et al.

Summary: Sixty primary care providers, registered nurses, licensed practical nurses, clerks, psychologists and social workers from a US veterans’ primary care pain management team participated in a semi-structured interview of nine focus groups to characterise provider’s perception of barriers to access nonpharmacological treatment for chronic pain. Opioid availability and access were at the core of perceptions of barriers to reducing opioid use and improving the use of nonpharmacological pain management therapies for chronic pain. Opioid availability and access were at the core of perceptions of barriers to reducing opioid use and improving nonpharmacological therapy use. Access barriers to nonpharmacological pain management therapy also included geographical, financial, temporal, cultural and digital factors.

Comment: This is a semi-structured interview of nine focus groups to characterise provider’s perception of barriers to access nonpharmacological treatment for chronic pain. At the system level, the geographical distance, patient out-of-pocket cost, and treatment delay appear to be the common themes. At the provider level, issues appear to be beliefs of increased provider workload, perception of patient resistance to change, and limitation of digital connectivity. Further studies on mitigating these access barriers are warranted.


Abstract

Impact of empathy in the patient-doctor relationship on chronic pain relief and quality of life

Authors: Cánovas L et al., Empathy Study Group

Summary: The impact of physician empathy, as perceived by patients with moderate-to-severe chronic pain, was prospectively evaluated in 2898 Spanish pain clinic attendees. Each participant was seen by the same physician at baseline, 1 month and 3 months. Significant decreases were seen for Brief Pain Inventory Short Form pain intensity scores over the 3-month period (p<0.001), with respective reductions for ratings of worst, least, average and current pain of 33.7%, 42.5%, 40.0% and 46.9%. Pain intensity scores decreased from 6.3 at baseline to 4.7 at 1 month and then to 3.8 at 3 months (p<0.050). There were also significant improvements in the EuroQol-5D tariff and VAS scores (p<0.001). A linear regression analysis revealed that Jefferson Scale of Patient Perceptions of Physician Empathy scores and Life Orientation Test – Revised scores were significantly associated with both pain relief and health-related QOL, whereas Pain Coping Questionnaire scores were not.

Comment: Previous studies have shown physician empathy benefits patients’ treatment outcomes. This is a prospective cohort study of 150 pain clinics in Spain showing slight but independent associations between patients’ perceptions of physician empathy (Jefferson Scale of Patient Perceptions of Physician Empathy) and changes in pain intensity and health-related QOL, using multiple linear regression models of the changes from baseline to 3 months. We know from previous study that empathy with patients with medically unexplained disorders is thought to reduce stigmatisation. Hence, this suggests that empathy is a component of clinical competence. It will be interesting to see local data.


Abstract

The impact of perceived injustice on pain-related outcomes: a combined model examining the mediating roles of pain acceptance and anger in a chronic pain sample

Authors: Carriere JS et al.

Summary: The potential for pain acceptance and anger to mediate the relationship between perceived injustice and adverse pain-related outcomes was explored in this cross-sectional study of 354 tertiary pain centre attendees with chronic pain who completed measures of perceived injustice, pain acceptance, anger, physical function, pain intensity and opioid use. Pain acceptance was found to fully mediate the relationship between perceived injustice and physical function, and also the relationship between perceived injustice and opioid use, and was a partial mediator of the relationship between perceived injustice and pain intensity.

Comment: Perceived injustice is defined as appraisal of severity and irreparability of pain-related losses, a sense of unfairness and blame. It has been shown to be a significant barrier to effective recovery. This is a cross-sectional study of chronic pain patients in a tertiary pain centre (n=354) showing that pain acceptance (CPAQ-8), but not anger (PROMIS anger), mediated the relationship between perceived injustice (IEQ) and physical function, and also between perceived injustice and opioid use, using multiple mediation analysis. It is possible that individuals with low pain acceptance are more likely to maintain disability behaviours to seek adequate retribution for losses, and use opioids for not only pain, but also distress. However, a previous study by Scott et al. showed that the state anger subscale of STAI mediated the relationship between perceived injustice and pain intensity. This study implied that it is important to integrate interventions to improve pain acceptance in the treatment programme.

Reference: Clin J Pain 2018;34:739–47

Abstract
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.
Transcranial alternating current stimulation at alpha frequency reduces pain when the intensity of pain is uncertain

Authors: Arendsen LJ et al.

Summary: This research explored the ability of somatosensory transcranial ACS (alternating current stimulation) at the alpha frequency (which allows the potential causal relationship between alpha activity and pain to be examined) to reduce pain experiences, and if this is influenced by uncertainty about pain intensity. Twenty-three participants were each subjected to both alpha-transcranial ACS and sham stimulation, during which their perceived pain intensity and unpleasantness were assessed; visual cues preceding pain stimuli were used to manipulate uncertainty. Significant transcranial ACS by uncertainty by stimulus intensity interactions were detected for both reported pain intensity and unpleasantness.

Comment: Alpha activity is an oscillatory neural activity at 8–13Hz. Higher prestimulus somatosensory alpha activity and resting alpha activity are associated with lower pain intensity. Placebo/expectancy-related pain relief is associated with increased resting alpha activity. This is a human experimental pain model using α-transcranial ACS (10Hz, 1mA) over the somatosensory cortex, showing significantly lower pain experience during α-transcranial ACS compared with sham stimulation when the participant was uncertain about the intensity of an upcoming pain stimulus. Battleday et al. theorises that α-transcranial ACS changes oscillatory activity in one region and hence the information processing of the neural network. I look forward to further study on alpha frequency.

Reference: J Pain 2018;19:807–18
Abstract

Ultrasound-guided percutaneous peripheral nerve stimulation: neuromodulation of the sciatic nerve for postoperative analgesia following ambulatory foot surgery

Authors: Ilfied BM

Summary: This proof-of-concept study set out to evaluate the feasibility of using percutaneous sciatic nerve stimulation to treat immediate postoperative pain in patients who had undergone ambulatory foot surgery. The participants received 2 minutes of active stimulation and sham stimulation in a randomised crossover design, followed by continuous stimulation until lead removal on postoperative days 14–28. A downward trajectory in pain was seen during the 5 minutes of active stimulation in the four participants who received this first, while the three who received the sham intervention initially experienced no change until their subsequent 5-minute stimulation crossover. All seven participants experienced a decrease in pain scores to 57% of baseline during the subsequent 30 minutes of stimulation. A continuous popliteal nerve block was provided for rescue analgesia for three participants during postoperative days 0–3. Resting and dynamic numerical rating scale pain scores averaged <1 and opioid use averaged <1 tablet per day with active stimulation. There was one lead dislodgement, two lead fractures during use and one lead fracture during intentional withdrawal.

Comment: This is a proof-of-concept study, using a randomised, double-masked controlled design (n=7) of percutaneous ultrasound, showing reduced pain and decrease opioid requirement after ambulatory hallux valgus surgery. No sensory deficits or motor block was detected. Stimulation was delivered at 100Hz, at sensory or motor threshold, with amplitude range of 0.2–2mA and pulse duration of 15–200 msec. Lead insertion was between sciatic bifurcation and supragluteal region. The author noted previous experience programmes, osseointegration and nursing home resident pain management.

Abstract

Comparison of effects of melatonin and gabapentin on post operative anxiety and pain in lumbar spine surgery

Authors: Javaherforoozshadef F et al.

Summary: Patients undergoing lumbar surgery with fixed method general anaesthesia were randomised to receive melatonin 6mg (n=30), gabapentin 600mg (n=30) or placebo (n=30), administered 100 minutes before surgery. Assessments of pain, satisfaction and anxiety were undertaken at 1, 2, 6, 12 and 24 hours post surgery, with anxiety also assessed 15 minutes before surgery. Compared with placebo, melatonin and gabapentin were both associated with significant differences in mean VAS scores (p=0.02) and a significant reduction in the intensity of anxiety (p=0.01).

Comment: Previous study has suggested an anxiolytic effect of preoperative melatonin, without mental dysfunction. There have been conflicting reports on its analgesic properties in the acute postoperative setting. This is a double-blinded, controlled, clinical study (n=90) showing preoperative melatonin or gabapentin is associated with reductions in anxiety (VAS) and pain (VAS) in lumbar surgery, at 12 hours and 24 hours. Melatonin 6mg, gabapentin 600mg or placebo was given 100 minutes before induction. Melatonin is thought to activate opioid receptors (hyperpolarisation due to potassium influx) and decrease cAMP formation in neurons. Furthermore, melatonin can reduce inflammation by reducing expression of lipoxigenase and cyclooxygenase.

Further validation studies with larger sample sizes are warranted.

Reference: Anesthesiology 2018;129:47–57
Abstract

Comparison of anterior suprascapular, suprascapular, and interscalene nerve block approaches for major outpatient arthroscopic shoulder surgery

Authors: Auyong DB et al.

Summary: Patients scheduled for arthroscopic shoulder surgery (n=189) were randomised to interscalene, suprascapular or anterior suprascapular block using 15mL of 0.5% ropivacaine in this trial, with a 1-point margin on an 11-point numerical rating pain scale set to define noninferiority. The mean postsurgery pain scores in the respective interscalene, suprascapular and anterior suprascapular groups were 1.9, 2.3 and 2.0, with differences of 0.4 between the suprascapular and interscalene groups (p=0.088 for noninferiority) and 0.1 between the suprascapular and interscalene groups (p=0.012 for noninferiority). Opioid consumption was similar among groups, while preservation of vital capacity was better in the anterior suprascapular and suprascapular groups compared with the interscalene group.

Comment: Interscalene block may be associated with phrenic nerve block, and symptomatic hemidiaphragmatic paralysis after shoulder surgery is challenging to treat. Siegenthaler et al. described selective anterior suprascapular block within the suprascapular fossa to avoid phrenic nerve paresis. This is a randomised, controlled, double-blind trial showing that anterior suprascapular block, but not suprascapular block, is noninferior to interscalene block for analgesia (VAS), and is superior in preserving pulmonary function (vital capacity) for major arthroscopic shoulder surgery. Patients with pre-existing lung dysfunction were excluded, but the data support anterior suprascapular block rather than interscalene block to lessen pulmonary side effects.

Reference: Anesthesiology 2018;129:47–57
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.

Abstract