The impact of anxiety and depression on the outcomes of chronic low back pain multidisciplinary pain management

Authors: Oliveira DS et al

Summary: The effectiveness of a typical multidisciplinary approach for managing chronic LBP was explored in a prospective cohort of 284 patients over 1 year following initial presentation to a multidisciplinary chronic pain clinic, with focus on the impact of anxiety and depression symptoms and their interactions with clinical outcomes. Most patients exhibited both anxiety and depression and experienced significantly greater pain severity and pain-related disability. Over time, anxiety and depression mainly predicted pain interference changes, and pain interference changes were significantly predicted by the interaction of anxiety and depressive symptoms.

Comment: Previous review has shown the efficacy of multidisciplinary treatment programmes in improving function and pain in chronic LBP, but the evidence for chronic pain patients with comorbid anxiety and depression has been lacking. This is a prospective multicentre cohort study (n=284) of nonspecific LBP patients in a noncontrolled clinical practice setting, showing the severity of anxiety and depression (HADS) at baseline negatively influenced the success of chronic LBP multidisciplinary treatment outcomes (BPI and S-TOPS) at 1-year follow-up. The interaction between anxiety and depression also showed a synergistic effect. The effect of anxiety and depression on treatment outcome was assessed using a linear mixed-effects model. I note that only functioning patients without severe and incapacitating psychiatric conditions were included, which may underestimate the effect. This cohort may need more intensive pain management, maybe in conjunction with other interventions. Further research is warranted.


Abstract

Pooled analysis of tanezumab efficacy and safety with subgroup analyses of phase III clinical trials in patients with osteoarthritis pain of the knee or hip

Authors: Tive L et al.

Summary: Pooled data from phase 3 clinical trials of tanezumab in moderate-to-severe knee or hip OA (osteoarthritis) were used to evaluate efficacy (four trials) and safety (nine trials) of this treatment. The studies compared active comparators (naproxen, celecoxib, diclofenac, oxicodone) or placebo with intravenous tanezumab either with or without oral naproxen, celecoxib or diclofenac. Tanezumab was associated with significant improvements for WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) pain and physical function and PGA (patient’s global assessment) of OA; subgroup analyses revealed similar efficacy in at-risk subgroups. Adverse events were most frequent when tanezumab was combined with a nonsteroidal anti-inflammatory drug. Adverse event incidences were similar between tanezumab monotherapy and active comparator groups and across subgroups, and were lowest with placebo. Tanezumab recipients experienced more abnormal peripheral sensation than placebo and active comparator recipients, and those who received active comparators had slightly more adverse events consistent with postganglionic sympathetic dysfunction.

Comment: This is a pooled analysis of phase 3 placebo-controlled clinical trials (n=6000) of tanezumab (5mg and 10mg, intravenous, 8 weekly) in patients with moderate-to-severe OA of the hip or knee, showing significantly improved pain and function (WOMAC) when compared with placebo and active comparator naproxen, and no increased adverse events for the at-risk group (diabetes, severe OA symptoms and >65 years of age). I note an increased incidence of reporting of abnormal sensation in the tanezumab group overall, which was found to be mononeuropathy or radiculopathy. It was postulated that tanezumab unmasked (rather than caused) underlying neuropathy, because neuromodulatory effects typically cause a length-dependent polyneuropathy picture, which was not the case. Furthermore, the diabetes subgroup did not have a higher incidence of these adverse events. I note that the adverse effects suggestive of postganglionic sympathetic dysfunction (e.g. orthostatic hypotension, nausea) were slightly higher in the tanezumab (4.8%) and the placebo groups (4.3%). Overall, tanezumab has the potential to be part of the chronic OA pain treatment armamentarium.


Abstract
New approach for investigating neuropathic allodynia by optogenetics

**Authors:** Fauda M

**Summary:** These authors reviewed recent studies that used optogenetics to provide evidence that optical stimulation of Aβ fibres and other low-threshold mechanoreceptors is sufficient to produce pain after peripheral nerve injury. Whole-cell recording showed that optical Aβ stimulation after nerve injury causes excitation of lamina I dorsal horn neurons that are usually silent after this type of stimulation, and Aβ stimulation after nerve injury was shown to activate central amygdaloid neurons and produce aversive behaviours. They conclude that optogenetics is a powerful approach for investigating low-threshold mechanoreceptor-derived pain (which resembles mechanical allodynia) with sensory and emotional features following nerve injury, and could assist in the discovery of new, effective drugs for treating neuropathic pain.

**Comment:** Previous study with von Frey filaments can activate both low-threshold mechanoreceptors and nociceptors, and cannot be used for in vitro studies (e.g. spinal cord slices). In optogenetics, neurons can be genetically modified to express light-sensitive ion channels, e.g. neuronal control can be achieved by optogenetic actuators, e.g. ChR2 (channelrhodopsin-2). Optogenetics allows precise manipulation of the activity of a defined cell population to study low-threshold mechanoreceptor-mediated pain, e.g. ChR2+ Aβ fibres. A recent study showed that optical stimulation of Aβ fibres in a rat model produces pain after peripheral nerve injury and elimination of mechanical hypersensitivity by ablation of these primary afferents, further elucidating the function of each type of primary afferent in allodynia-like response, i.e. Aβ or C/Aδ low-threshold mechanoreceptors. Furthermore, a recent RNA sequencing study showed 15 excitatory and 15 inhibitory spinal dorsal horn neurons. Looking at how Aβ fibres activate the spinal dorsal horn lamina I neurons will be interesting. Further advances in optogenetics, e.g. optimisation of opsins, may also allow neuromodulation by facilitating stable and long-lasting control of neural activity.

Reference: Pain 2019;160:S53–8

**Abstract**

Intravenous lidocaine provides similar analgesia to intravenous morphine for undifferentiated severe pain in the emergency department

**Authors:** Clattenburg EJ et al.

**Summary:** Intravenous lignocaine, dosed according to bodyweight, and intravenous morphine were compared for efficacy for severe pain (NRS score ≥7) in adults presenting to ED in this pilot, unblinded RCT. Lignocaine recipients could receive rescue morphine. There was no significant difference between the lignocaine and morphine arms for mean pain NRS score at 60 minutes (5.1 and 4.2, respectively; absolute difference, 0.9 (95% CI –1.2 to 2.9); the respective side effect rates were 13% and 38% and the respective patient satisfaction rates were 87% and 4.2, respectively. There was no significant difference in the frequency of adverse events between the two groups. The study authors concluded that intravenous lignocaine was noninferior to intravenous morphine for pain reduction and satisfaction at 1 hour. Intravenous lignocaine, when offered as the first-line analgesia, is likely to be preferred by patients over rescue morphine.

**Comment:** There are sparse data for use of intravenous lignocaine in the ED, with a previous study suggesting efficacy and safety for renal colic, acute radicular back pain and acute limb ischaemia. This is a pilot, unblinded RCT (n=32) for patients with undifferentiated severe pain in the ED, showing that intravenous lignocaine was noninferior to intravenous morphine for pain reduction and satisfaction at 1 hour. Intravenous lignocaine, when offered as the first-line analgesia, reduced the need for an opioid in 19% of patients and reduced morphine utilisation by 47%. Intravenous lignocaine (1.5 mg/kg in 100 mL normal saline) was given as a loading bolus over 10 minutes, followed by 50-minute infusions at the same dose. A previous study of intravenous lignocaine for neuropathic pain as high as 500 mg over 30 minutes (6.7 mg/kg for a 75 kg patient over 30 minutes) showed only dose-dependent minor side effects and no dysrhythmia. However, local anaesthetic toxicity still needs to be monitored while maintaining the therapeutic range (2.5–3.5 µg/mL). Toxicity usually begins when the plasma concentration exceeds 9 µg/mL with neurological symptoms and CV collapse at plasma concentrations greater than 10 µg/mL. Further study is warranted.


**Abstract**

Intrathecal betamethasone for cancer pain: a study of its analgesic efficacy and safety

**Authors:** Taguchi H et al.

**Summary:** Patients with opioid-resistant cancer pain (n=104) were treated with lumbar intrathecal betamethasone 2 mg or 3 mg once per week for 28 days in this study. Pain relief was recorded for both the lower and upper halves of the participants’ bodies. Compared with participants whose most severe pain was due to metastases distal from the vertebral column, those with vertebral column and/or surrounding nerve plexus metastases causing the most severe pain were significantly more likely to experience immediate analgesia and a greater decrease in NRS score at day 1, and significantly greater proportions reported analgesia at 7 days (59% vs. 6%) and 28 days (71% vs. 31%). There were no adverse effects related to neurotoxicity.

**Comment:** Betamethasone was administered together with an anticancer drug, such as cytarabine, intrathecal to enhance the anticancer action for meningial cancer. Previous case reports have suggested unexpected analgesia of intrathecal betamethasone in intractable cancer pain. This is a prospective cohort study (n=104) of cancer patients with severe opioid-resistant pain, showing intrathecal betamethasone (Rinderon) produced an analgesic effect for intractable pain in the short term and the long term (28 days), especially from vertebral column and surrounding nerve plexus metastases, without signs of neurological toxicity. Betamethasone 2 mg or 3 mg was given weekly for 4 weeks. The postulated mechanism of betamethasone includes nuclear action (modulation of nuclear transcription and protein synthesis) and action on membrane-bound receptors. Glucocorticoids have also been shown to induce apoptosis of cancer cells through activation of the mitochondrial caspase pathway. Further study is warranted.


**Abstract**

Safety and tolerability of fremanezumab for the prevention of migraine

**Authors:** Silberstein SD et al.

**Summary:** These authors pooled safety data from four phase 2b and 3, 16-week, placebo-controlled, clinical trials investigating fremanezumab in patients with chronic or episodic migraine. 1704 participants were randomised to receive fremanezumab, which they received for a mean of 83.8 days, and 862 were randomised to placebo. Seventy-eight participants elected to withdraw from the trials, 60 were lost to follow-up and 50 withdrew because of adverse events. Most adverse events were mild to moderate, and affected 48–69% of participants from the treatment groups. Injection-site reactions were the most common adverse events which were considered to be unrelated to the study drug. CV adverse events, abnormal liver function tests and hypersensitivity were uncommon, and they affected similar proportions of fremanezumab and placebo recipients.

**Comment:** Preventative treatment for migraine is commonly limited by poor adherence due to lack of efficacy and intolerable side effects. Fremanezumab is a humanised monoclonal antibody that targets CGRP. A previous pivotal trial has demonstrated the effectiveness of monthly or quarterly fremanezumab for the prevention of chronic migraine and episodic migraine, including two phase 3 RCTs (HALO) and two phase 2b RCTs. This is a pooled analysis of safety data of four placebo-controlled phase 2b and 3 RCTs (n=2566) showing safety and tolerability, with mostly mild-to-moderate side effects, mostly injection-site reactions. The total exposure was 390.4 patient-years and the maximum exposure was 181 days. CGRP acts as a vasodilator in the CV system, and antagonism of the system raises sympathetic activity and provokes headaches. They conclude that fremanezumab is a safe and effective treatment for chronic or episodic migraine.

Reference: Headache; Published online April 12, 2019

**Abstract**

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• Significantly greater improvement in functional outcomes† vs. oxycodone CR.†,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)

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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; concomitant administration of other mu-opioid receptor agonist analgesics, general anaesthetics, phenothiazines, other tranquilisers, antihistamines, antidepressants or other CNS depressants (including alcohol and illicit drugs); patients who are receiving MAO inhibitors or who have withdrawn from MAO inhibitors within the last 14 days.

ADVERSE EFFECTS: Very common (≥1/10): dizziness, somnolence, headache, nausea, constipation. Common (≥1/100 to <1/10): Decreased appetite, anxiety, depressed mood, sleep disorders, nervousness, dyspepsia, disturbance in attention, tremor, muscle contractions involuntary, flushing, dyspnoea, vomiting, diarrhoea, dysuria, 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, whole with sufficient liquid, approximately every twelve hours, with or without food. Initiation of therapy in patients currently not taking opioids analgesics: start with 50 mg PALEXIA SR twice daily. Initiation of therapy in patients currently taking opioid analgesics: monitor 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 twice daily every 3 days shown to be appropriate in most patients in clinical trials. Total daily doses > 300 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.


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Chemotherapy-induced peripheral neuropathy: where are we now?

Author: Colin LA

Summary: This review of CIPN (chemotherapy-induced peripheral neuropathy) concluded that a strong translational approach is most likely to engender success when addressing this problem. The authors highlighted the need for well-designed preclinical studies that reflect clinical situations wherever possible, combined with careful consideration of clinical trial design. They also emphasised the importance of co-operation for the standardisation of assessment techniques, ensuring that there is robust validation of the methods used across a wide range of mechanisms of CIPN. A range of targets for novel therapies has been identified but the authors also highlighted the need for holistic approaches that consider nonpharmacological interventions.

Comment: CIPN is common, with an incidence of up to 30% at 6 months for neurotoxic chemotherapy. It is a predominantly sensory neuropathy in a glove-stocking distribution, although autonomic and fine motor function can also be affected. Histologically, there is a loss of sensory fibres and reduced intradermal nerve fibre density. Some sensory profiles can be more chemotherapy-specific (e.g. cold hypersensitivity with platinum-based therapy). Duoxetine is the only agent with sufficient evidence for recommendation (ASCO), but there is also limited evidence for tricyclic antidepressants and gabapentin. There are multiple underlying CIPN mechanisms, which offer multiple pharmacotherapeutic targets. Increased Na+/ channels, decreased K+ channels and increased Cav3.2 were found with CIPN. Mitochondrial dysfunction was also identified, including increased mitochondrial p53, HDAC (histone deacetylase-6; disrupting axonal mitochondrial capacity) and increased reactive oxygen species. Central glial cells and peripheral immune cells may also contribute. Preclinical study also showed the role of L-10 in the recovery of platinum and taxane-related CIPN. Further collaborative work on standardised assessments and translational therapeutic approaches is needed.

Reference: Pain 2019;160:S1–10

Abstract

CGRP and the trigeminal system in migraine

Authors: Iyengar S et al.

Summary: This narrative review updates the role of CGRP within the trigeminovascular system in migraine pathophysiology. The authors concluded that CGRP has an essential role in the pathophysiology of migraine, and that treatments that interfere with CGRP function in the peripheral trigeminal system are effective for treating migraine; migraine attacks may be prevented by blocking sensitisation of the trigeminal nerve by attenuating CGRP activity in the periphery. The authors noted that this therapeutic strategy may also have potential for cluster headache.

Comment: The understanding of the pathophysiology of migraine and CGRP has progressed in the last decade. Oscillation in hypothalamic activity and increased cortical excitability can activate the trigeminovascular system to release CGRP from trigeminal afferent neurons (CGRP-ergic C fibres nociceptors). CGRP is also released by the activated trigeminal nerve ending due to cortical spreading depression (causing liberation of extracellular K+), hydrogen and proinflammatory substance from glial cells and nerve terminals). CGRP sensitises the trigeminal primary afferent Aδ fibres. CGRP also acts on endothelial CGRP receptors producing vasodilatation, triggering endothelial NOS and NO production (from satellite cells, astrocytes and secondary neurons). NO can enhance non-CGRP neuron activity, and further release of CGRP. CGRP activates astrocytes to release inflammatory mediators, and activates secondary neurons by increasing excitatory neurotransmitters, e.g. glutamates. Second-order neuron activity is thus enhanced due to these complex processes (central sensitisation). Although CGRP does not directly excite trigeminal nucleus caudalis neurons, it causes peripheral sensitisation ofafferent Aδ fibres and peripheral C fibres (by cross-excitation).

Reference: Headache 2019;59:659–81

Abstract

Illicit fentanyls in the opioid street market: desired or imposed?

Authors: Mars SG et al.

Summary: These authors discussed potential causes for the worldwide increase in illicitly manufactured fentanyl and its analogues, asking if users can identify fentanyl, do they desire it, and if so, can they express this demand in a way that influences the supply. They found that the current evidence suggests a supply-led addition of fentanyl to the illicit drug market, mainly as a result of heroin supply shocks and shortages, changes in the availability of prescription opioids and reduced costs and risks to suppliers. The authors identified an apparent lack of knowledge regarding fentanyl’s presence in purchased illicit drugs and access to fentanyl-free alternatives among current users in the US, Canada and Europe.

Comment: Nonprescription fentanyl and analogues (disguising as heroin or counterfeit prescription pills) have been shown to increase overdose mortality. The current evidence suggests that this is related to the heroin supply shortage, changing opioid prescription availability and reduced cost (as compared with heroin) to suppliers. There is limited evidence to suggest that some users can identify and desire fentanyl, and retail sales do not have sufficient choice to produce demand-led change. The question is, how would this change clinical practice? Nonprescription fentanyl was thought to be more difficult to antagonise with buprenorphine, with clients experiencing euphoria using nonprescription fentanyl whilst on a therapeutic dose of buprenorphine. A higher dose of methadone was thought to be required for greater craving reduction and cross-tolerance blockade. Theoretically, parental naloxone might be more effective than an intranasal route, given the rapid onset of nonprescription fentanyl-induced overdose. Further research to guide treatment in this group of patients is needed.


Abstract

The role of sleep quality and fatigue on the benefits of an interdisciplinary treatment for adults with chronic pain

Authors: de la Vega R et al.

Summary: How changes in sleep quality and fatigue impact on the benefits of a 4-week interdisciplinary chronic pain treatment was explored in 125 adults with chronic pain. The pain intensity benefits of the programme were found to be significantly, independently affected by changes in fatigue and sleep disturbances; improvements in fatigue were found to be predictive of improvements in depressive symptoms, and pretreatment and pre- to post-treatment decreases in pain intensity (one of the control variables) were predictive of improvements in disability.

Comment: Interdisciplinary pain programmes have been shown to improve pain intensity and disability. However, the specific mediating factor is not well understood. This is a prospective cohort study (n=125) of chronic pain patients in a 4-week interdisciplinary pain management programme, showing the change in fatigue and sleep (PROMIS-29 subscale) predicted treatment-related benefit in pain intensity, depression and disability. Regression analysis was used to determine correlation (not causality). The moderate-to-large percentage of the variance explained by the model suggests a significant association. I note mediation was not assessed. This would support further exploration of a sleep-specific component of the treatment programme. However, further validation study with a larger sample size is needed.


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.