Novel drug treatments for pain in advanced cancer and serious illness: a focus on neuropathic pain and chemotherapy-induced peripheral neuropathy

Palliative Care & Social Practice

2024, Vol. 18: 1–18

DOI: 10.1177/26323524241266603

Mellar P. Davis

***Abstract*:** Drugs that are commercially available but have novel mechanisms of action should be explored as analgesics. This review will discuss haloperidol, miragabalin, palmitoylethanolamide (PEA), and clonidine as adjuvant analgesics or analgesics. Haloperidol is a sigma-1 receptor antagonist. Under stress and neuropathic injury, sigma-1 receptors act as a chaperone protein, which downmodulates opioid receptor activities and opens several ion channels. Clinically, there is only low-grade evidence that haloperidol improves pain when combined with morphine, methadone, or tramadol in patients who have cancer, pain from fibrosis, radiation necrosis, or neuropathic pain. Miragabalin is a gabapentinoid approved for the treatment of neuropathic pain in Japan since 2019. In randomized trials, patients with diabetic neuropathy have responded to miragabalin. Its long binding half-life on the calcium channel subunit may provide an advantage over other gabapentinoids. PEA belongs to a group of endogenous bioactive lipids called ALIAmides (autocoid local injury antagonist amides), which have a sense role in modulating numerous biological processes in particular non-neuronal neuroinflammatory responses to neuropathic injury and systemic inflammation. Multiple randomized trials and meta-analyses have demonstrated PEA's effectiveness in reducing pain severity arising from diverse pain phenotypes. Clonidine is an alpha2 adrenoceptor agonist and an imidazoline2 receptor agonist, which is U.S. Federal Drug Administration approved for attention deficit hyperactivity disorder in children, Tourette's syndrome, adjunctive therapy for cancer-related pain, and hypertension. Clonidine activation at alpha2 adrenoceptors causes downstream activation of inhibitory G-proteins (Gi/Go), which inhibits cyclic Adenosine monophosphate (AMP) production and hyperpolarizes neuron membranes, thus reducing allodynia. Intravenous clonidine has been used in terminally ill patients with poorly controlled symptoms, in particular pain and agitation.

Keywords: clonidine, haloperidol, miragabalin, pain, palmitoylethanolamide

Received: 23 January 2024; revised manuscript accepted: 19 June 2024.

Introduction

The improvement in life expectancy of patients with cancer and the common use of chemotherapy agents such as paclitaxel and oxaliplatin for lung, breast, pancreatic, colorectal, esophageal, and prostate cancer has led to a significant prevalence of neuropathic pain among patients living with cancer or in cancer survivorship.[1] Bortezomib, Revlimid, and vinca alkaloids cause neuropathic sensory and motor symptoms in patients treated for hematologic malignancies.[2–6] In addition to chemotherapy, other anti-cancer treatments, including surgery and radiation therapy, may cause chronic pain, with a subset of patients experiencing neuropathic pain. Since cancer occurs in an older population, many patients have comorbid illnesses such as diabetes and may have had neuropathic pain before their

Correspondence to:
Mellar P. Davis
Geisinger Commonwealth School of Medicine, 100 North Academy Avenue, Danville, PA 17822, USA
mdavis2@geisinger.edu

cancer, which is worsened with treatment. Effective analgesics for cancer-induced neuropathic pain (CIPN) are few and far between. Duloxetine is the only analgesic that has demonstrated benefit in a randomized controlled trial. Gabapentin is ineffective.[7] Pregabalin lacks a randomized trial that tests its benefit against a placebo.

Neuropathic pain, in general, is difficult to treat.[8] There are a limited number of analgesic options outside of effective opioids. Tricyclic antidepressants and gabapentinoids are the main class of adjuvants used to treat neuropathic pain. Tricyclic antidepressants have significant side effects, and gabapentin and pregabalin potentiate the respiratory depression and sedation associated with opioids.[9–13] Gabapentinoids are subject to abuse potential and have a "drug-liking" effect. Novel agents with distinctly different mechanisms of action are needed and can genotype the mechanism causing the pain. Trials to validate may require a transition to mechanistically informed, personalized, and stratified trials.[14]

Recent studies based upon preclinical animal models have used established medications with novel targets as analgesics for neuropathic pain, including CIPN. These drugs are haloperidol, miragabalin (available in Japan). palmitoylethanolamide (PEA), and clonidine. Each of these commercially available medications has a target that causes improved pain behaviors in animals (antinociception) or reduces pain severity in humans (analgesia). Miragabalin has analgesic mechanisms similar to gabapentinoids but has a distinctly different interaction with voltage-gated calcium channels that improve gabapentinoid responses and reduce side effects.

Neuropathic pain, which arises from damage to somatosensory neurons, is clinically manifested by allodynia (pain from innocuous stimuli), hyperalgesia (exaggerated response to usually painful stimuli), and spontaneous or continuous pain described as paresthesia or dysesthesia, or lightening-like unprovoked pain.[15–17] The correlation between animal pain behaviors and subjective pain responses in clinical trials is imperfect and sometimes leads to disappointing results in clinical trials. Each drug discussed in this review requires more rigorous clinical trial data before being adopted into standard practice.

Haloperidol

Introduction

Physicians know haloperidol as a classic antipsychotic that binds to D2 (dopamine) receptors, which are of questionable benefit in treating delirium but are an effective antiemetic.[18,19] Very few are aware that haloperidol is a high-affinity irreversible sigma-1 receptor antagonist with analgesic potential.[20–24]

Mechanism of action

Sigma-1 receptors are a unique class of receptors distinct from opioid receptors, single transmembrane receptors on the endoplasmic reticulum (ER) on mitochondria-associated membranes.[25] In specific neurons (such as those at the spinal cord), sigma-1 receptors are clustered at ER membranes that abut postsynaptic plasma membranes.[26] Under stress and neuropathic injury, sigma-1 receptors act as a chaperone protein, which downmodulates opioid receptor activities and opens several ion channels, exerting a role in pain transmission.[27–31] This presents a target to treat neuropathic pain.[32] Sigma-1 receptors are over-expressed in neuropathic pain and, when tonically active, are "anti-opioid" for mu (MOR) and kappa (KOR) receptors.[21,22,33,34] Activation of sigmoid-1 receptors reduces pain thresholds under pathologic conditions such as nerve injury but not in normal circumstances.[35] Hence, sigma-1 receptor antagonists are unlikely to be effective in treating acute pain, but multiple preclinical studies have demonstrated that haloperidol reduces neuropathic pain behaviors in animals.[28,36–42]

Preclinical studies

Chemotherapeutic-induced neuropathic pain is reported to reduce sigma-1 receptor levels in the spinal cord. Paclitaxel-exposed Chinese hamster ovarian cells caused overexpression of sigma-1 receptors in clusters. In one study, the sigma-1 receptor agonist SA4503 inhibited neuropathy induced by oxaliplatin and paclitaxel. In a second study, a sigma-1 receptor antagonist given before paclitaxel reduced neuropathic pain in animals by preventing the upregulation of extracellular signal-regulated kinases.[43,44] Fluvoxamine, a sigma-1 receptor inducer and agonist, significantly reduced paclitaxel neuropathic pain and neurotoxicity.[45–47] Furthermore, activation of the

sigma1R is necessary for developing the sensory nerve mitochondrial damage and neuropathic pain caused by paclitaxel.[48] More preclinical studies are needed to explain the opposite findings found in these preclinical studies.

Preclinical studies: Comparison with gabapentin and morphine

Haloperidol is a very potent noncompetitive sigmoid-1 receptor blocker that has been shown to enhance gabapentin opioid analgesia in preclinical models and case studies.[36,38,49–56] In a chronic constrictive injury neuropathic model, male Wistar rats responded better to haloperidol than gabapentin. The combination of gabapentin and haloperidol produced synergistic antinociception.[49] Haloperidol does not increase pain response latencies in normal rats but extends latencies to tail-flick responses in neuropathically injured animals.[57] Haloperidol was given before morphine in animal models; dose-dependently improves the antinociceptive effect of morphine and reduces physical dependence.[36,58]

Clinical studies

Clinically, there is only low-grade evidence that haloperidol improves pain when combined with morphine, methadone, or tramadol in patients who have cancer, pain from fibrosis, radiation necrosis, or neuropathic pain.[51,55,56,59,60] Two clinical studies confirmed the lack of benefit of haloperidol when treating acute pain.[61,62]

Evidence of potential clinical benefits from other sigma-1 receptor blockers for neuropathic pain

There is sufficient preclinical evidence and some low-grade clinical experience to suggest that haloperidol may be an effective analgesic for neuropathic pain as an adjuvant to opioid therapy. MR309, a novel selective sigma-1 receptor ligand, reduced the proportion of patients with severe chronic neuropathy (3.0% vs 18.2% with placebo; $p = 0.046$). The total amount of oxaliplatin delivered was greater in the active arm, however. In an animal model, the sigma-1 receptor antagonists BD-1063 or S1RA given 30 min before each paclitaxel dose prevented the development of cold and mechanical allodynia in mice.

Rationale for haloperidol in chemotherapy-related neuropathy

The acute administration of both sigma-1 receptor antagonists dose-dependently reversed both types of paclitaxel-induced chronic allodynia. Therefore, it would be reasonable to propose a randomized trial of haloperidol versus placebo or the combination of haloperidol plus duloxetine versus duloxetine alone in patients receiving either paclitaxel or oxaliplatin chemotherapy, with neuropathic pain as the primary outcome, and nausea and vomiting as secondary outcomes.

Rationale for combining haloperidol with morphine or gabapentin for cancer-related neuropathic pain

In patients with cancer neuropathic pain, a randomized trial of an opioid versus an opioid plus haloperidol or gabapentin/pregabalin alone versus gabapentin/pregabalin plus haloperidol should be considered. In preclinical studies, haloperidol did not increase the lethality of morphine. As a result, the combination of morphine and haloperidol may be safer than the combination of morphine and gabapentin.[63] There may be a concern about combining methadone and haloperidol since both prolong the QTc interval. However, torsades de pointe from haloperidol occurs mostly at doses greater than 3 mg/day.[64–66]

Pharmacokinetics: The dose needed for analgesia

What haloperidol dose is needed to block sigma-1 receptors? In humans, haloperidol occupancy of sigma-1 receptors is high at relatively low doses.[67] A dose of 10 mg by mouth occupies 65% of dopamine (D2) receptors, whereas a 3 mg binds to 80% of the central nervous system (CNS) sigma-1 receptors.[68,69] Haloperidol does not downmodulate sigma-1 receptor mRNA, so recovery will occur when the drug is stopped.[70] A reduced haloperidol metabolite also readily crosses the CNS, binding and blocking sigma-1 receptors.[71]

Side effects

Extrapyramidal side effects, including akathisia, bradykinesia, Parkinsonism, and tremor, can occur in 10% of treated individuals. Elevated liver function tests, depression, dizziness, and sedation (at high doses) occur in less than 10%. Prolongation of the QTc and torsades de pointes

and the neuroleptic malignant syndrome occur in less than 0.1%.

Mirogabalin besylate

Introduction

Miragabalin is a gabapentinoid approved for the treatment of neuropathic pain in Japan since 2019.

Mechanism of action

So how is mirogabalin different from gabapentin and pregabalin, and why would it improve analgesia when neuropathic pain is unresponsive to other gabapentinoids? Similar to pregabalin, pregabalin is a ligand for the voltage-gated calcium channel subunit alpha2/delta1 and alpha2/delta2. Mirogabalin, like pregabalin, blocks presynaptic voltage-gated calcium channels, which prevents neurotransmitter release across the synapse.[72] The alpha2/delta1 subunit is upregulated in somatosensory dorsal horn neurons with neuropathic injury.[73] In CIPN, the alpha2/delta2 complexes with an-methyl-D-aspartate receptors through the C-tail of the calcium channel unit, which increases the neurotransmitter traffic across the synapse.[74] The result is enhanced excitatory postsynaptic responses significantly curtailed by mirogabalin.[75]

Pharmacodynamic differences between miragabalin and other gabapentinoids

Mirogabalin differs from pregabalin in several ways. Mirogabalin dissociates from the alpha2/delta1 subunit more slowly than gabapentin and pregabalin and is more selective for alpha2/delta1 than alpha2/delta2.[72] The dissociation constant (Kd) is four times lower than pregabalin (13.5 nM vs 62.5 nM), demonstrating a greater affinity and five times lower for the alpha2 delta2 subunit (22.7 nM vs 125 nM).[76,77] Dissociation from alpha2/delta2 is 11.1 h, whereas it is 1.4 h for pregabalin.[76] The relative duration of binding differences between alpha2/delta1 and alpha2/delta2 between mirogabalin and pregabalin, which favors mirogabalin alpha2/delta1 interactions, may be an important margin to efficacy, benefits, and side effects.[76] Alpha2/delta2 binding leads to gabapentinoid side effects, and alpha2/delta1 binding is necessary for analgesia.[78] Supratherapeutic doses (fourfold to sevenfold) of mirogabalin are needed before experiencing a "drug-liking" effect, whereas" drug-like" effects of pregabalin occur at therapeutic doses.[79]

Clinical studies

In randomized trials involving 834 patients with diabetic neuropathy, miragabalin 30 mg daily significantly reduced pain over 14 weeks ($p = 0.027$), and analgesia was sustained over 52 weeks without serious side effects. Treatment-emergent side effects (somnolence, edema, and weight gain) occurred in 27%.[80] In a second study of 763 patients with post-herpetic neuralgia, treatment mirogabalin doses of 15, 20, and 30 mg/day over 14 weeks. The pain was significantly improved over the placebo. A 52-week open extension of the study demonstrated no analgesic tolerance. Treatment emerging side effects occurred in 39.7%.[81] A third study involved 150 patients with spinal cord injury. Progressive mirogabalin doses from 10 to 30 mg daily significantly reduced pain intensity ($p = 0.0001$). The odds of experiencing a 30% reduction in pain was 1.91, and a 50% reduction at 2.52.[82] A fourth study involved 210 patients with central neuropathic pain. The dose was 15 mg twice daily. The short form of the McGill pain questionnaire significantly improved. Adverse effects were similar to those in other studies, including somnolence, edema, and dizziness.[83]

Comparison with other gabapentinoids

Mirogabalin has been compared to pregabalin in the treatment of CIPN and retrospective studies of patients with pancreatic cancer and oxaliplatin-induced neuropathy. Mirogabalin doses ranging from 10 to 30 mg daily and pregabalin doses of 75 to 150 mg/day were compared. Though baseline neuropathic pain was worse in those started on mirogabalin, pain significantly improved with miragabalin over 6 weeks (92.3%) compared with pregabalin (33.3%).[84] In a single-arm prospective study involving 52 patients treated with paclitaxel, mirogabalin 10–30 mg daily reduced numerical rating scores (0 no pain, 10 severe pain) by 30%, with a mean change of 1.7 points.[85] Mirogabalin has reduced pain, whereas pregabalin has failed to reduce pain or cause side effects, limiting pregabalin dosing.[84,86]

Disadvantages to mirogabalin

There are disadvantages to mirogabalin. Mirogabalin does not effectively reduce pain

associated with fibromyalgia.[87,88] Opioids do not appear to improve mirogabalin analgesia but do increase adverse effects.[77,89] Alcohol, benzodiazepines, and tramadol increase sedation when combined with mirogabalin.[90]

Pharmacokinetics

Mirogabalin is 85% bioavailable, with peak concentrations (T-max) occurring approximately 1 h after oral intake. The mean terminal plasma half-life ranges between 2.57 and 3.08 h, but as mentioned, the clinical effects are long-lasting due to its binding time to alpha2/delta1 receptors, so it is given twice daily.[91] Oral dosage forms available in Japan are 2.5, 5, 10, and 15 mg. The starting dose is 5 mg twice daily, slowly titrated over 45 days to a maximum of 15 mg twice daily, depending on response.[92] No dose adjustments are needed for a creatinine clearance greater than 50 mL/min per 1.73 m^2. Doses should be adjusted to 50% of normal for a creatinine clearance of 30–50 ml/min per 1.73 m^2 and 25% or a creatinine clearance of less than 30 mL/min per 1.73 m^2.[93] Doses do not need to be adjusted for mild to moderate hepatic impairment.[94] Mirogabalin does not interact with cytochrome P450 enzymes but is a substrate for organic anion transporter 1 and 2, organic cation transporter 2, and multidrug and toxin extrusion transporters.[95]

Side effects

The adverse effects commonly encountered with mirogabalin are dizziness (8%–16%), somnolence (6%–24%), and headache (6%–14%). Constipation, diarrhea, edema, fatigue, nausea, vomiting, and weight gain have rare side effects.[96]

Future randomized trials should include a comparison of miragabalin with duloxetine for CIPN.

Palmitoylethanolamide

Introduction

PEA belongs to a group of endogenous bioactive lipids called ALIAmides (autocoid local injury antagonist amides), which have a sense role in modulating numerous biological processes, particularly non-neuronal neuroinflammatory responses to neuropathic injury and systemic inflammation.[97–102]

Mechanism of action

PEA accumulates in tissues as a biological response to inflammation and increases in brain regions involved in nociception and the spinal cord in response to neurologic injury and inflammation.[102–110] PEA is formed from cell membranes in response to stress. The "on-demand" production targets mast cell activation, degranulation, and microglial responses to nerve injury. Downstream, it inhibits cytokine release and intra-nuclear transit of NF-κB, which prevents interleukin, tumor necrosis factor, and prostaglandin responses.[97,102,105,110–118] There is a delicate balance between ALIAmide lipid responses to neuropathic injury and the subsequent neuroinflammatory response to injury, determining neuropathic pain experiences.[98]

PEA targets multiple receptors as a modulator of pain

PEA has multiple targets: the orphan receptor GPR-55 as the principal one, vanilloid receptors, particularly TRPV-1 (the capsaicin receptor), and does indirectly interact with classical cannabinoid receptors (CB1, CB2) through increased anandamide levels (through competition with fatty acid amide hydrolase) and inhibits glutamatergic neurotransmission.[119–126] However, most evidence suggests that the antiallodynic and antihyperalgesic effects are related to peroxisome proliferator-activated receptor (PPAR) activation and mast cell degranulation and activation inhibition.[105,111,113,127–134] PPARs are a family of nuclear receptors that modulate inflammation by down-regulating inflammatory gene responses, thus impairing chemokine expression. PPAR agonists are a new class of analgesics that target non-neuronal reactions to neuropathic injury.[135,136]

Preclinical studies

Multiple animal models have demonstrated the benefits of PEA in neuropathic injury. PEA reduced hypersensitivity to mechanical and thermal stimuli in neuropathically injured animals, and this reduction was dependent on PPAR and classic cannabinoid receptors.[137] PEA in mice subjected to chronic constrictive injury-related neuropathic pain delayed mast cell recruitment and degranulation, abolished nerve growth factor activation, preserved the constricted nerve from degeneration, and reduced microglia numbers in the spinal cord, associated with pain reduction.[138]

PEA improved the pain behaviors associated with selective nerve injury in Sprague Dawley rats.[139]

PEA and preclinical studies of chemotherapy neuropathy

PEA has been effective in reducing CIPN in animals. Animals exposed to oxaliplatin were treated with PEA 30 mg/kg intraperitoneal. PEA prevented the hypersensitivity associated with oxaliplatin. In the spinal cord, there was reduced glia activation and improved neuropathic pain behaviors without interfering with oxaliplatin anticancer activity.[129] In a second model, PEA (10 mg/kg) reduced pain behaviors from oxaliplatin, reduced hyperactive glia in the spinal cord, and prevented proinflammatory cytokine release from the spinal cord. This was due to the downmodulation of the NF-κB pathway.[140] PEA reduced spinal cord and hippocampal neuroinflammation in animals exposed to paclitaxel. The PEA doses were 30 mg/kg. PEA also had an antianxiety and antidepressant effect noted in animals. The benefits were dependent upon the presence of PPAR and CB1 receptors.[141] Two other studies have demonstrated the benefits of PEA in preventing and treating paclitaxel-related pain in animals.[142,143]

Clinical studies

Clinical studies have demonstrated the benefits of PEA. A randomized controlled trial compared PEA 600 mg/day with a placebo and found that patients with diabetic neuropathy improved in pain, sleep, and depression associated with reductions in circulating Il-6 and C-reactive protein (CRP). No side effects were noted.[144] A second study involving patients with diabetic neuropathy used PEA 300 mg twice daily in a prospective study. There was a dramatic reduction in pain ($p < 0.00001$) without any adverse events or safety issues.[145] A recent clinical study involved patients receiving neoadjuvant oxaliplatin or paclitaxel with neuropathy. They received a PEA supplement for 3 months. Motor and sensory subjective outcomes were measured. Objective neurologic outcomes included deep tendon reflexes and vibratory perception. After 3 months, the overall clinical benefit, which included stability or improvement, occurred in 64%–77% of patients. Objective improvement occurred in 40% of the paclitaxel patients and 31% of the oxaliplatin-treated patients. Deep tendon reflexes improved by 20% and 16.9%, respectively. The quality of life improved in 22%–24% of patients with oxaliplatin, and 37.5%–45.9% of patients treated with paclitaxel. Only 6%–15% were treated with other analgesics.[146]

A large number of clinical studies have used PEA for inflammatory or neuropathic pain with positive outcomes. Four recently published meta-analyses have demonstrated that PEA is an effective analgesic with side effects no greater than placebo compared to randomized trials.[147–150]

PEA in combination with other analgesics

PEA has been used in combination with other analgesics. In preclinical models, PEA improves opioid analgesia and delays analgesic tolerance.[151,152] PEA improves gabapentin and paracetamol analgesia.[151,153]

Advantages to PEA

In all randomized trials, PEA had the same side effects as placebo.[144,154,155] PEA improves psychological depression and fatigue associated with COVID-19.[156–158] PEA in randomized trials is an effective adjuvant to the treatment of autism.[159,160]

Pharmacokinetics

The pharmacokinetics of PEA are unknown. PEA has a high first-pass clearance as a highly lipophilic compound.[124] The intestinal wall and liver contain hydrolytic enzymes involved in PEA metabolism. Micronized or ultra-micronized ultramicronized PEA appears to improve animal absorption.[161] The volume of distribution is quite large. PEA readily crosses into the CNS, accumulates within cells, and passes through cell membranes.[124,162] PEA binds to fatty acid binding protein 5 and thus competes for binding with anandamide. Also, PEA competes with anandamide metabolism by fatty acid amide hydrolase, thus increasing anandamide intracellular levels.[124] PEA is also metabolized by *N*-acylethanolamine acid amidase to palmitic acid and ethanolamine.[124] There are no known drug–drug interactions reported with PEA.

There is significant preclinical evidence that PEA may effectively treat CIPN and prevent its occurrence. One non-placebo controlled trial suggests that there are clinical benefits. Presently, a placebo-controlled randomized controlled study tests PEA 400 or 800 mg daily for 8 weeks versus placebo in patients with established CIPN. A

similar trial in patients receiving oxaliplatin or paclitaxel as either an adjuvant or neoadjuvant treatment for their cancer should be considered.

Side effects

PEA has no known side effects.

Clonidine

Introduction

Clonidine is an alpha2 adrenoceptor agonist and an imidazoline2 receptor agonist, which is U.S. Federal Drug Administration approved for attention deficit hyperactivity disorder in children, Tourette's syndrome, adjunctive therapy for cancer-related pain, and hypertension.[163–165] There is a growing body of literature that suggests that clonidine may be an effective analgesic for neuropathic pain.[166–169] There is extensive evidence that perioperative clonidine is an effective analgesic in children, is opioid-sparing, and is associated with reduced postoperative nausea and vomiting.[170–177] We will not review spinal clonidine, as it is a common practice in interventional pain management, but will limit discussions to parenteral, topical, oral, and transdermal clonidine, particularly for pain.

Mechanism of action

Clonidine binds to imidazoline receptors within the CNS and causes hypertension. It also has anti-arrhythmogenic activity and activates alpha2 adrenoceptors, causing sedation.[178] Both receptors may be involved in analgesia.[179–181] Clonidine preferentially binds to alpha2 rather than alpha1 adrenoceptors (200–1), so sedation occurs at low doses, but as clonidine doses are increased, anxiety may occur due to binding to alpha1 receptors.[182–184]

Clonidine may reduce pain by several different mechanisms. Clonidine binds to nor adrenergic receptors descending in the dorsal lateral funiculus, which inhibits incoming sensory nociceptive neurotransmission at the level of the dorsal horn.[185,186] Within the intermediolateral column of the dorsal horn, there is a dense population of alpha2 adrenoceptors on myelinated Ac and unmyelinated C fibers which inhibit excitatory neurotransmission within the dorsal horn.[187] Neurologic injury increases the expression of alpha2 adrenoceptors in the dorsal root ganglion sensory neurons, which are then targeted by clonidine.[188] Depending on the subtype of alpha2 adrenoceptors, activation of these presynaptic receptors inhibits the release of substance P, calcitonin gene-related protein, and glutamate.[189,190] Clonidine inhibits nerve sprouting from neuropathic injury.[191,192]

Clonidine activation at alpha2 adrenoceptors causes downstream activation of inhibitory G-proteins (Gi/Go), which inhibits cyclic adenosine monophosphate (AMP) production and hyperpolarizes neuron membranes, thus reducing allodynia.[193–195] In this way, clonidine may be synergistic with opioid analgesia.[195] Clonidine also reduces the expression of the vanilloid receptor TRPV1, which is upregulated with neuropathic injury and contributes to hyperalgesia and allodynia.[196] Finally, clonidine does appear to downmodulate neuroinflammatory responses to neural injury.[197–200]

Preclinical studies

There are preclinical neuropathic pain models which demonstrate synergistic analgesia between clonidine and opioids.[201–204] Synergy has also been reported with acetaminophen and *N*-methyl-D-aspartate receptor blockers.[205–207] One of the advantages of a clonidine/opioid combination is that clonidine does not potentiate the respiratory depression of opioids, unlike gabapentinoids.[208,209]

There is preclinical evidence that clonidine reduces pain behaviors in animals with oxaliplatin and vincristine neuropathy.[210–212] CIPN pain behaviors induced in male Wistar rats by paclitaxel injections were significantly improved with clonidine.[213] The benefits appeared to be related to increased descending noradrenergic activity at the spinal cord level. Preclinical studies suggest that clonidine may reduce CIPN associated with oxaliplatin and paclitaxel. Clinical studies are needed to confirm preclinical findings.

Clinical studies

Oral. Clonidine (0.1 mg oral) has improved low-dose gabapentin analgesia in diabetic individuals with painful neuropathy.[166] Oral clonidine 0.1–0.2 mg by mouth has been compared to zolpidem in patients with chronic pain and secondary insomnia. Clonidine's time to sleep onset was quicker ($p = 0.001$), and pain was significantly improved relative to zolpidem. Sleep quality was

better, and there was no amnesia, confusion, or falls with clonidine.[214]

Transdermal. Transdermal clonidine has been used for diabetic neuropathy. A small underpowered crossover trial found that transdermal clonidine 0.3 mg/day was tolerable and reduced pain as a trend but not significantly so (−13%, 95% confidence interval −29% to +3%).[215] The "trend" needs to be validated in a large, well-controlled trial. A second study using an enrichment enrollment design using the same dose and route found that clonidine reduced pain by 20% (95% confidence interval +4% to +35%) in a group of patients with diabetic neuropathic pain.[216]

Intravenous. Intravenous clonidine has been used in terminally ill patients with poorly controlled symptoms, in particular pain and agitation. One report initiated clonidine at 75 µg IV and titrated to response (maximum dose 1200 µg/day).[217] A similar group of patients was initially treated with 75–150 µg intravenous in patients with refractory pain to opioids or refractory agitation to antipsychotics and benzodiazepine. Doses were adjusted to response. Of 115 patients treated, 85 responded.[218]

Clonidine as an adjuvant analgesic

Clonidine is an understudied adjuvant analgesic. Clonidine is versatile, with options for parenteral, topical, oral, and transdermal administration. There is evidence that clonidine improves opioid analgesia without adversely influencing respiratory function and may reduce opioid analgesic tolerance. Clonidine also reduces opioid withdrawal symptoms. A combination of analgesia and improved sleep without benzodiazepine side effects suggests that clonidine may be a preferred sleeping medication for those individuals with chronic pain in palliative medicine or on opioids.

Pharmacokinetics

Oral clonidine is highly bioavailable, with peak concentrations between 60 and 90 min. It is 30%–40% protein bound and has a volume of distribution of 3.2–5.6 L/kg.[219] This reflects its lipophilicity and wide distribution. It rapidly crosses into the CNS. Less than 50% is inactivated in the liver. There are no known active metabolites. Between 40% and 60% of clonidine is excreted by the kidneys unchanged. Renal failure increases the half-life from 12–16 to 24 h.[219]

Adverse effects of clonidine

Clonidine's side effects include drowsiness, hypotension, dry mouth, and sexual dysfunction. In comparison with oral clonidine, transdermal clonidine reduces the incidence and severity of such symptomatic side effects as dry mouth, drowsiness, and sexual dysfunction. Minor skin reactions occur at the application site of the transdermal patch with moderate frequency. Adherence to transdermal clonidine therapy is high, and patients commonly prefer it to oral therapy.[220]

Conclusion

Haloperidol, miragabalin, PEA, and clonidine have unique mechanisms that may effectively reduce neuropathic pain. Combinations with standard adjuvants should be explored. In addition, haloperidol on clonidine may be opioid-sparing, improving analgesia and reducing opioid tolerance. The benefits of the commercially available medications, haloperidol, PEA, and clonidine, should be explored further in randomized trials.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution

Mellar P. Davis: Conceptualization; Formal analysis; Writing – original draft; Writing – review & editing.

Acknowledgements

Janet Hardy for her review of the concept and direction in preparing the manuscript.

Funding

The author received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The author is the primary investigator of a trial involving palmitoylethanolamide in treating chemotherapy-induced neuropathy (ACCRU-SC-2102) through a Mayo Clinic grant. The author has received no direct funding from the grant.

Availability of data and materials
Not applicable.

ORCID iD
Mellar P. Davis https://orcid.org/0000-0002-7903-3993

References

1. Moloney NA and Lenoir D. Assessment of neuropathic pain following cancer treatment. *Anat Rec (Hoboken)* 2024; 307(2): 309–319.
2. Mackereth P and Stringer J. Living with chemotherapy-induced peripheral neuropathy: a nested qualitative study. *Br J Nurs* 2023; 32(20): 978–986.
3. Molinares D, Kurtevski S and Zhu Y. Chemotherapy-induced peripheral neuropathy: diagnosis, agents, general clinical presentation, and treatments. *Curr Oncol Rep* 2023; 25(11): 1227–1235.
4. de Miranda Drummond PL, Dos Santos RMM, Silveira LP, et al. Chemotherapy-induced peripheral neuropathy impacts quality of life and activities of daily living of Brazilian multiple myeloma patients. *Curr Drug Saf*. Epub ahead of print August 2023. DOI: 10.2174/1574886318666230817162424.
5. Sreeram K, Seaton R, Greenwald MK, et al. Chemotherapy-induced peripheral neuropathy in the Detroit research on cancer survivors (ROCS) cohort. *Cancer Causes Control* 2023; 34(5): 459–468.
6. Chen CS and Hertz DL. Chemotherapy-induced peripheral neuropathy. *Handb Exp Pharmacol* 2023; 277: 299–337.
7. Rao RD, Michalak JC, Sloan JA, et al. Efficacy of gabapentin in the management of chemotherapy-induced peripheral neuropathy: a phase 3 randomized, double-blind, placebo-controlled, crossover trial (N00C3). *Cancer* 2007; 110(9): 2110–2118.
8. Hammond EA, Pitz M, Lambert P, et al. Quantitative sensory profiles of upper extremity chemotherapy induced peripheral neuropathy: are there differences in sensory profiles for neuropathic versus nociceptive pain? *Can J Pain* 2019; 3(1): 169–177.
9. Akbar MF, Ikram A and Naeem A. Increasing trends in abuse of gabapentin in drug addicts in rural population of Punjab. *J Coll Physicians Surg Pak* 2023; 33(1): 120.
10. Evoy KE, Sadrameli S, Contreras J, et al. Abuse and misuse of pregabalin and gabapentin: a systematic review update. *Drugs* 2021; 81(1): 125–156.
11. Gabapentin and risk of severe respiratory depression. *Drug Ther Bull* 2018; 56(1): 3–4.
12. Ongley D, Hayward AK and Allan C. Severe respiratory depression associated with perioperative opioid-sparing gabapentin use. *Anaesth Intensive Care* 2014; 42(1): 136–137.
13. Adverse reactions to the tricyclic-antidepressant drugs. Report from Boston Collaborative Drug Surveillance Program. *Lancet* 1972; 1(7749): 529–531.
14. Soliman N, Kersebaum D, Lawn T, et al. Improving neuropathic pain treatment—by rigorous stratification from bench to bedside. *J Neurochem*. Epub ahead of print February 2023. DOI: 10.1111/jnc.15798.
15. Dosenovic S, Nikolic Z, Ivancev B, et al. Awareness and acceptability of Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials core outcome set for chronic pain among surveyed neuropathic pain authors. *J Comp Eff Res* 2019; 8(9): 671–683.
16. Finnerup NB, Sindrup SH and Jensen TS. Chronic neuropathic pain: mechanisms, drug targets and measurement. *Fundam Clin Pharmacol* 2007; 21(2): 129–136.
17. Merskey H. The taxonomy of pain. *Med Clin North Am* 2007; 91(1): 13–20, vii.
18. Davis M, Hui D, Davies A, et al. MASCC antiemetics in advanced cancer updated guideline. *Support Care Cancer* 2021; 29(12): 8097–8107.
19. Agar MR, Lawlor PG, Quinn S, et al. Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliative care: a randomized clinical trial. *JAMA Intern Med* 2017; 177(1): 34–42.
20. Kim FJ and Pasternak GW. Sigma(1) receptor ligand binding: an open-and-shut case. *Nat Struct Mol Biol* 2018; 25(11): 992–993.
21. Pasternak GW. Allosteric modulation of opioid g-protein coupled receptors by sigma(1) receptors. *Handb Exp Pharmacol* 2017; 244: 163–175.
22. Mei J and Pasternak GW. Modulation of brainstem opiate analgesia in the rat by sigma 1 receptors: a microinjection study. *J Pharmacol Exp Ther* 2007; 322(3): 1278–1285.
23. Chien CC and Pasternak GW. Functional antagonism of morphine analgesia by (+)-pentazocine: evidence for an anti-opioid sigma 1 system. *Eur J Pharmacol* 1993; 250(1): R7–R8.

24. Cobos EJ, del Pozo E and Baeyens JM. Irreversible blockade of sigma-1 receptors by haloperidol and its metabolites in guinea pig brain and SH-SY5Y human neuroblastoma cells. *J Neurochem* 2007; 102(3): 812–825.

25. Davis MP. Sigma-1 receptors and animal studies centered on pain and analgesia. *Expert Opin Drug Discov* 2015; 10(8): 885–900.

26. Hayashi T. Sigma-1 receptor: the novel intracellular target of neuropsychotherapeutic drugs. *J Pharmacol Sci* 2015; 127(1): 2–5.

27. Ortiz-Renteria M, Juarez-Contreras R, Gonzalez-Ramirez R, et al. TRPV1 channels and the progesterone receptor Sig-1R interact to regulate pain. *Proc Natl Acad Sci U S A* 2018; 115(7): E1657–E1666.

28. Arena E, Dichiara M, Floresta G, et al. Novel sigma-1 receptor antagonists: from opioids to small molecules: what is new? *Future Med Chem* 2018; 10(2): 231–256.

29. Merlos M, Romero L, Zamanillo D, et al. Sigma-1 receptor and pain. *Handb Exp Pharmacol* 2017; 244: 131–161.

30. Soriani O and Rapetti-Mauss R. Sigma 1 receptor and ion channel dynamics in cancer. *Adv Exp Med Biol* 2017; 964: 63–77.

31. Hayashi T, Kagaya A, Takebayashi M, et al. Modulation by sigma ligands of intracellular free Ca++ mobilization by N-methyl-D-aspartate in primary culture of rat frontal cortical neurons. *J Pharmacol Exp Ther* 1995; 275(1): 207–214.

32. Denaro S, Pasquinucci L, Turnaturi R, et al. Sigma-1 receptor inhibition reduces mechanical allodynia and modulate neuroinflammation in chronic neuropathic pain. *Mol Neurobiol* 2024; 61(5): 2672–2685.

33. Chien CC and Pasternak GW. Selective antagonism of opioid analgesia by a sigma system. *J Pharmacol Exp Ther* 1994; 271(3): 1583–1590.

34. Mei J and Pasternak GW. Molecular cloning and pharmacological characterization of the rat sigma1 receptor. *Biochem Pharmacol* 2001; 62(3): 349–355.

35. Kim HW, Roh DH, Yoon SY, et al. Activation of the spinal sigma-1 receptor enhances NMDA-induced pain via PKC- and PKA-dependent phosphorylation of the NR1 subunit in mice. *Br J Pharmacol* 2008; 154(5): 1125–1134.

36. Mena-Valdes LC, Blanco-Hernandez Y, Espinosa-Juarez JV, et al. Haloperidol potentiates antinociceptive effects of morphine and disrupt opioid tolerance. *Eur J Pharmacol* 2021; 893: 173825.

37. Deciga-Campos M, Melo-Hernandez LA, Torres-Gomez H, et al. Design and synthesis of N-(benzylpiperidinyl)-4-fluorobenzamide: a haloperidol analog that reduces neuropathic nociception via sigma(1) receptor antagonism. *Life Sci* 2020; 245: 117348.

38. Espinosa-Juarez JV, Jaramillo-Morales OA and Lopez-Munoz FJ. Haloperidol decreases hyperalgesia and allodynia induced by chronic constriction injury. *Basic Clin Pharmacol Toxicol* 2017; 121(6): 471–479.

39. Cobos EJ, Entrena JM, Nieto FR, et al. Pharmacology and therapeutic potential of sigma(1) receptor ligands. *Curr Neuropharmacol* 2008; 6(4): 344–366.

40. Entrena JM, Cobos EJ, Nieto FR, et al. Antagonism by haloperidol and its metabolites of mechanical hypersensitivity induced by intraplantar capsaicin in mice: role of sigma-1 receptors. *Psychopharmacology (Berl)* 2009; 205(1): 21–33.

41. Cendan CM, Pujalte JM, Portillo-Salido E, et al. Antinociceptive effects of haloperidol and its metabolites in the formalin test in mice. *Psychopharmacology (Berl)* 2005; 182(4): 485–493.

42. Mei J and Pasternak GW. Sigma1 receptor modulation of opioid analgesia in the mouse. *J Pharmacol Exp Ther* 2002; 300(3): 1070–1074.

43. Tomohisa M, Junpei O, Aki M, et al. Possible involvement of the Sigma-1 receptor chaperone in chemotherapeutic-induced neuropathic pain. *Synapse* 2015; 69(11): 526–532.

44. Nieto FR, Cendan CM, Sanchez-Fernandez C, et al. Role of sigma-1 receptors in paclitaxel-induced neuropathic pain in mice. *J Pain* 2012; 13(11): 1107–1121.

45. Omi T, Tanimukai H, Kanayama D, et al. Fluvoxamine alleviates ER stress via induction of Sigma-1 receptor. *Cell Death Dis* 2014; 5(7): e1332.

46. Hashimoto K and Furuse T. Sigma-1 receptor agonist fluvoxamine for delirium in older adults. *Int J Geriatr Psychiatry* 2012; 27(9): 981–983.

47. Tanimukai H and Kudo T. Fluvoxamine alleviates paclitaxel-induced neurotoxicity. *Biochem Biophys Rep* 2015; 4: 202–206.

48. Nieto FR, Cendan CM, Canizares FJ, et al. Genetic inactivation and pharmacological blockade of sigma-1 receptors prevent paclitaxel-induced sensory-nerve mitochondrial abnormalities and neuropathic pain in mice. *Mol Pain* 2014; 10: 11.

49. Deciga-Campos M, Villafan-Gutierrez R, Espinosa-Juarez JV, et al. Synergistic interaction between haloperidol and gabapentin in a model of neuropathic nociception in rat. *Eur J Pharmacol* 2021; 891: 173702.

50. Negro S, Martin A, Azuara ML, et al. Stability of tramadol and haloperidol for continuous subcutaneous infusion at home. *J Pain Symptom Manage* 2005; 30(2): 192–199.

51. Shir Y, Shenkman Z and Kaplan L. Neuropathic pain unrelieved by morphine, alleviated by haloperidol [in Hebrew]. *Harefuah* 1990; 118(8): 452–454.

52. Raft D, Toomey T and Gregg JM. Behavior modification and haloperidol in chronic facial pain. *South Med J* 1979; 72(2): 155–159.

53. Ghaderi-Bafti F, Zarghami M, Ahmadi A, et al. Effectiveness and safety of haloperidol add-on methadone in acute opium withdrawal symptoms of opioid-dependent patients: a double-blind randomized placebo-controlled clinical trial. *Addict Health* 2021; 13(2): 85–94.

54. Cobos EJ and Baeyens JM. Use of very-low-dose methadone and haloperidol for pain control in palliative care patients: are the sigma-1 receptors involved? *J Palliat Med* 2015; 18(8): 660.

55. Salpeter SR, Buckley JS and Bruera E. The use of very-low-dose methadone for palliative pain control and the prevention of opioid hyperalgesia. *J Palliat Med* 2013; 16(6): 616–622.

56. Breivik H and Rennemo F. Clinical evaluation of combined treatment with methadone and psychotropic drugs in cancer patients. *Acta Anaesthesiol Scand Suppl* 1982; 74: 135–140.

57. Chien CC and Pasternak GW. Sigma antagonists potentiate opioid analgesia in rats. *Neurosci Lett* 1995; 190(2): 137–139.

58. Yang C, Chen Y, Tang L, et al. Haloperidol disrupts opioid-antinociceptive tolerance and physical dependence. *J Pharmacol Exp Ther* 2011; 338(1): 164–172.

59. Daw JL and Cohen-Cole SA. Haloperidol analgesia. *South Med J* 1981; 74(3): 364–365.

60. Maltbie AA and Cavenar JO Jr. Haloperidol and analgesia: case reports. *Mil Med* 1977; 142(12): 946–948.

61. Heard K, Bebarta VS, Hoppe JA, et al. Does administration of haloperidol or ketorolac decrease opioid administration for abdominal pain patients? A retrospective study. *Am J Emerg Med* 2020; 38(3): 517–520.

62. Masoumi K, Delirrooyfard A and Salehzadeh M. Comparison of the analgesic effects of haloperidol with or without morphine in patients with acute renal colic: a randomized double-blind clinical trial study. *Am J Emerg Med* 2019; 37(8): 1422–1427.

63. Hatoum NS and Davis WM. Morphine lethality in rats: effects of various central receptor blocking agents. *Res Commun Chem Pathol Pharmacol* 1979; 24(2): 251–257.

64. O'Brien JM, Rockwood RP and Suh KI. Haloperidol-induced torsade de pointes. *Ann Pharmacother* 1999; 33(10): 1046–1050.

65. Sharma ND, Rosman HS, Padhi ID, et al. Torsades de Pointes associated with intravenous haloperidol in critically ill patients. *Am J Cardiol* 1998; 81(2): 238–240.

66. Stepkovitch K, Heagle Bahn C and Gupta R. Low-dose haloperidol-associated QTc prolongation. *J Am Geriatr Soc* 2008; 56(10): 1963–1964.

67. Toyohara J, Sakata M and Ishiwata K. Imaging of sigma1 receptors in the human brain using PET and [11C]SA4503. *Cent Nerv Syst Agents Med Chem* 2009; 9(3): 190–196.

68. Ishiwata K, Oda K, Sakata M, et al. A feasibility study of [11C]SA4503-PET for evaluating sigmal receptor occupancy by neuroleptics: the binding of haloperidol to sigma1 and dopamine D2-like receptors. *Ann Nucl Med* 2006; 20(8): 569–573.

69. Bernardo M, Parellada E, Lomena F, et al. Double-blind olanzapine vs. haloperidol D2 dopamine receptor blockade in schizophrenic patients: a baseline-endpoint. *Psychiatry Res* 2001; 107(2): 87–97.

70. Inoue A, Sugita S, Shoji H, et al. Repeated haloperidol treatment decreases sigma(1) receptor binding but does not affect its mRNA levels in the guinea pig or rat brain. *Eur J Pharmacol* 2000; 401(3): 307–316.

71. Korpi ER, Kleinman JE, Costakos DT, et al. Reduced haloperidol in the post-mortem brains of haloperidol-treated patients. *Psychiatry Res* 1984; 11(3): 259–269.

72. Calandre EP, Rico-Villademoros F and Slim M. Alpha(2)delta ligands, gabapentin, pregabalin and mirogabalin: a review of their clinical pharmacology and therapeutic use. *Expert Rev Neurother* 2016; 16(11): 1263–1277.

73. Zajaczkowska R, Mika J, Leppert W, et al. Mirogabalin—a novel selective ligand for the alpha2delta calcium channel subunit. *Pharmaceuticals (Basel)* 2021; 14(2): 112.

74. Deng M, Chen SR, Chen H, et al. alpha2delta-1-Bound N-methyl-D-aspartate receptors

mediate morphine-induced hyperalgesia and analgesic tolerance by potentiating glutamatergic input in rodents. *Anesthesiology* 2019; 130(5): 804–819.

75. Kato J, Inoue T, Yokoyama M, et al. A review of a new voltage-gated Ca(2+) channel alpha(2) delta ligand, mirogabalin, for the treatment of peripheral neuropathic pain. *Expert Opin Pharmacother* 2021; 22(17): 2311–2322.
76. Domon Y, Arakawa N, Inoue T, et al. Binding characteristics and analgesic effects of mirogabalin, a novel ligand for the alpha(2)delta subunit of voltage-gated calcium channels. *J Pharmacol Exp Ther* 2018; 365(3): 573–582.
77. Chen EY, Beutler SS, Kaye AD, et al. Mirogabalin as a novel gabapentinoid for the treatment of chronic pain conditions: an analysis of current evidence. *Anesth Pain Med* 2021; 11(6): e121402.
78. Javed S, Alam U and Malik RA. Mirogabalin and emerging therapies for diabetic neuropathy. *J Pain Res* 2018; 11: 1559–1566.
79. Mendell J, Levy-Cooperman N, Sellers E, et al. Abuse potential of mirogabalin in recreational polydrug users. *Ther Adv Drug Saf* 2019; 10: 2042098619836032.
80. Baba M, Kuroha M, Ohwada S, et al. Results of mirogabalin treatment for diabetic peripheral neuropathic pain in Asian subjects: a phase 2, double-blind, randomized, placebo-controlled, study. *Pain Ther* 2020; 9(1): 261–278.
81. Kato J, Matsui N, Kakehi Y, et al. Mirogabalin for the management of postherpetic neuralgia: a randomized, double-blind, placebo-controlled phase 3 study in Asian patients. *Pain* 2019; 160(5): 1175–1185.
82. Ushida T, Katayama Y, Hiasa Y, et al. Mirogabalin for central neuropathic pain after spinal cord injury: a randomized, double-blind, placebo-controlled, phase 3 study in Asia. *Neurology* 2023; 100(11): e1193–e1206.
83. Ushida T, Katayama Y, Hiasa Y, et al. Long-term safety and efficacy of mirogabalin for central neuropathic pain: a multinational, phase 3, 52-week, open-label study in Asia. *Pain Ther* 2023; 12(4): 963–978.
84. Sugimoto M, Takagi T, Suzuki R, et al. Drug treatment for chemotherapy-induced peripheral neuropathy in patients with pancreatic cancer. *Fukushima J Med Sci* 2022; 68(1): 1–10.
85. Misawa S, Denda T, Kodama S, et al. Efficacy and safety of mirogabalin for chemotherapy-induced peripheral neuropathy: a prospective single-arm trial (MiroCIP study). *BMC Cancer* 2023; 23(1): 1098.
86. Sugimoto M, Takagi T, Suzuki R, et al. Mirogabalin vs pregabalin for chemotherapy-induced peripheral neuropathy in pancreatic cancer patients. *BMC Cancer* 2021; 21(1): 1319.
87. Merante D. The mirogabalin ALDAY phase 3 program in pain associated with fibromyalgia: the lessons learned. *Curr Med Res Opin* 2020; 36(4): 661–666.
88. Arnold LM, Whitaker S, Hsu C, et al. Efficacy and safety of mirogabalin for the treatment of fibromyalgia: results from three 13-week randomized, double-blind, placebo- and active-controlled, parallel-group studies and a 52-week open-label extension study. *Curr Med Res Opin* 2019; 35(10): 1825–1835.
89. Zajaczkowska R, Rojewska E, Ciechanowska A, et al. Mirogabalin decreases pain-like behaviours and improves opioid and ketamine antinociception in a mouse model of neuropathic pain. *Pharmaceuticals (Basel)* 2022; 15(1): 88.
90. Jansen M, Mendell J, Currie A, et al. Pharmacokinetics, pharmacodynamics, safety, and tolerability of mirogabalin when coadministered with lorazepam, zolpidem, tramadol, or ethanol: results from drug-drug interaction studies in healthy subjects. *Clin Pharmacol Drug Dev* 2018; 7(6): 597–612.
91. Toyama K, Eto T, Suzuki K, et al. Pharmacokinetics and bioequivalence of mirogabalin orally disintegrating tablets and conventional tablets in healthy Japanese participants. *Clin Pharmacol Drug Dev* 2023; 12(10): 985–990.
92. Kato K, Kodama S, Shiosakai K, et al. Relationship between the dose titration and adherence of mirogabalin in patients with peripheral neuropathic pain depending on renal function: a nationwide electronic medical record database study. *Expert Opin Pharmacother* 2023; 24(2): 267–282.
93. Yin OQ, Merante D, Truitt K, et al. Population pharmacokinetic modeling and simulation for assessing renal impairment effect on the pharmacokinetics of mirogabalin. *J Clin Pharmacol* 2016; 56(2): 203–212.
94. Duchin K, Senaldi G, Warren V, et al. Open-label single-dose study to assess the effect of mild and moderate hepatic impairment on the pharmacokinetics of mirogabalin. *Clin Drug Investig* 2018; 38(11): 1001–1009.

95. Tachibana M, Yamamura N, Atiee GJ, et al. Coadministration of probenecid and cimetidine with mirogabalin in healthy subjects: a phase 1, randomized, open-label, drug-drug interaction study. *Br J Clin Pharmacol* 2018; 84(10): 2317–2324.

96. Burgess J, Javed S, Frank B, et al. Mirogabalin besylate in the treatment of neuropathic pain. *Drugs Today (Barc)* 2020; 56(2): 135–149.

97. Petrosino S and Di Marzo V. The pharmacology of palmitoylethanolamide and first data on the therapeutic efficacy of some of its new formulations. *Br J Pharmacol* 2017; 174(11): 1349–1365.

98. Petrosino S and Schiano Moriello A. Palmitoylethanolamide: a nutritional approach to keep neuroinflammation within physiological boundaries—a systematic review. *Int J Mol Sci* 2020; 21(24): 9526.

99. Petrosino S, Schiano Moriello A, Cerrato S, et al. The anti-inflammatory mediator palmitoylethanolamide enhances the levels of 2-arachidonoyl-glycerol and potentiates its actions at TRPV1 cation channels. *Br J Pharmacol* 2016; 173(7): 1154–1162.

100. Della Rocca G and Re G. Palmitoylethanolamide and related ALIAmides for small animal health: state of the art. *Biomolecules* 2022; 12(9): 1186.

101. Cuzzocrea S and Crupi R. To go where nature leads: focus on palmitoylethanolamide and related ALIAmides as innovative approach to neuroinflammatory and pain-related disease states in honor of Doctor Francesco Della Valle. *Biomolecules* 2023; 13(11): 1583.

102. D'Amico R, Impellizzeri D, Cuzzocrea S, et al. ALIAmides update: palmitoylethanolamide and its formulations on management of peripheral neuropathic pain. *Int J Mol Sci* 2020; 21(15): 5330.

103. Balvers MG, Verhoeckx KC, Meijerink J, et al. Measurement of palmitoylethanolamide and other N-acylethanolamines during physiological and pathological conditions. *CNS Neurol Disord Drug Targets* 2013; 12(1): 23–33.

104. Luongo L, Guida F, Boccella S, et al. Palmitoylethanolamide reduces formalin-induced neuropathic-like behaviour through spinal glial/microglial phenotypical changes in mice. *CNS Neurol Disord Drug Targets* 2013; 12(1): 45–54.

105. Skaper SD and Facci L. Mast cell-glia axis in neuroinflammation and therapeutic potential of the anandamide congener palmitoylethanolamide. *Philos Trans R Soc Lond B Biol Sci* 2012; 367(1607): 3312–3325.

106. Ghafouri N, Ghafouri B, Larsson B, et al. High levels of N-palmitoylethanolamide and N-stearoylethanolamide in microdialysate samples from myalgic trapezius muscle in women. *PLoS One* 2011; 6(11): e27257.

107. Scuderi C, Esposito G, Blasio A, et al. Palmitoylethanolamide counteracts reactive astrogliosis induced by beta-amyloid peptide. *J Cell Mol Med* 2011; 15(12): 2664–2674.

108. Re G, Barbero R, Miolo A, et al. Palmitoylethanolamide, endocannabinoids and related cannabimimetic compounds in protection against tissue inflammation and pain: potential use in companion animals. *Vet J* 2007; 173(1): 21–30.

109. Lambert DM, Vandevoorde S, Jonsson KO, et al. The palmitoylethanolamide family: a new class of anti-inflammatory agents? *Curr Med Chem* 2002; 9(6): 663–674.

110. D'Aloia A, Molteni L, Gullo F, et al. Palmitoylethanolamide modulation of microglia activation: characterization of mechanisms of action and implication for its neuroprotective effects. *Int J Mol Sci* 2021; 22(6): 3054.

111. Skaper SD, Facci L and Giusti P. Glia and mast cells as targets for palmitoylethanolamide, an anti-inflammatory and neuroprotective lipid mediator. *Mol Neurobiol* 2013; 48(2): 340–352.

112. Skaper SD, Facci L, Fusco M, et al. Palmitoylethanolamide, a naturally occurring disease-modifying agent in neuropathic pain. *Inflammopharmacology* 2014; 22(2): 79–94.

113. Skaper SD, Facci L, Barbierato M, et al. N-Palmitoylethanolamine and neuroinflammation: a novel therapeutic strategy of resolution. *Mol Neurobiol* 2015; 52(2): 1034–1042.

114. Skaper SD. Impact of inflammation on the blood-neural barrier and blood-nerve interface: from review to therapeutic preview. *Int Rev Neurobiol* 2017; 137: 29–45.

115. Petrosino S, Cordaro M, Verde R, et al. Oral ultramicronized palmitoylethanolamide: plasma and tissue levels and spinal anti-hyperalgesic effect. *Front Pharmacol* 2018; 9: 249.

116. Impellizzeri D, Cordaro M, Bruschetta G, et al. N-palmitoylethanolamine-oxazoline as a new therapeutic strategy to control neuroinflammation: neuroprotective effects in experimental models of spinal cord and brain injury. *J Neurotrauma* 2017; 34(18): 2609–2623.

117. D'Aloia A, Arrigoni F, Tisi R, et al. Synthesis, molecular modeling and biological evaluation of metabolically stable analogues of the endogenous fatty acid amide palmitoylethanolamide. *Int J Mol Sci* 2020; 21(23): 9074.

118. D'Agostino G, La Rana G, Russo R, et al. Central administration of palmitoylethanolamide reduces hyperalgesia in mice via inhibition of NF-kappaB nuclear signalling in dorsal root ganglia. *Eur J Pharmacol* 2009; 613(1–3): 54–59.

119. Di Marzo V, Melck D, Orlando P, et al. Palmitoylethanolamide inhibits the expression of fatty acid amide hydrolase and enhances the anti-proliferative effect of anandamide in human breast cancer cells. *Biochem J* 2001; 358(Pt 1): 249–255.

120. De Petrocellis L, Davis JB and Di Marzo V. Palmitoylethanolamide enhances anandamide stimulation of human vanilloid VR1 receptors. *FEBS Lett* 2001; 506(3): 253–256.

121. Hussain Z, Uyama T, Tsuboi K, et al. Mammalian enzymes responsible for the biosynthesis of N-acylethanolamines. *Biochim Biophys Acta Mol Cell Biol Lipids* 2017; 1862(12): 1546–1561.

122. Ueda N, Tsuboi K and Uyama T. Metabolism of endocannabinoids and related N-acylethanolamines: canonical and alternative pathways. *FEBS J* 2013; 280(9): 1874–1894.

123. Im DS. GPR119 and GPR55 as receptors for fatty acid ethanolamides, oleoylethanolamide and palmitoylethanolamide. *Int J Mol Sci* 2021; 22(3): 1034.

124. Rankin L and Fowler CJ. The basal pharmacology of palmitoylethanolamide. *Int J Mol Sci* 2020; 21(21): 7942.

125. Bellanti F, Bukke VN, Moola A, et al. Effects of ultramicronized palmitoylethanolamide on mitochondrial bioenergetics, cerebral metabolism, and glutamatergic transmission: an integrated approach in a triple transgenic mouse model of Alzheimer's disease. *Front Aging Neurosci* 2022; 14: 890855.

126. Skaper SD, Buriani A, Dal Toso R, et al. The ALIAmide palmitoylethanolamide and cannabinoids, but not anandamide, are protective in a delayed postglutamate paradigm of excitotoxic death in cerebellar granule neurons. *Proc Natl Acad Sci U S A* 1996; 93(9): 3984–3989.

127. Zhou G, Fu X, Wang L, et al. Palmitoylethanolamide ameliorates neuroinflammation via modulating PPAR-alpha to promote the functional outcome after intracerebral hemorrhage. *Neurosci Lett* 2022; 781: 136648.

128. Ye S, Chen Q, Jiang N, et al. PPARalpha-dependent effects of palmitoylethanolamide against retinal neovascularization and fibrosis. *Invest Ophthalmol Vis Sci* 2020; 61(4): 15.

129. Di Cesare Mannelli L, D'Agostino G, Pacini A, et al. Palmitoylethanolamide is a disease-modifying agent in peripheral neuropathy: pain relief and neuroprotection share a PPAR-alpha-mediated mechanism. *Mediators Inflamm* 2013; 2013: 328797.

130. Khasabova IA, Xiong Y, Coicou LG, et al. Peroxisome proliferator-activated receptor alpha mediates acute effects of palmitoylethanolamide on sensory neurons. *J Neurosci* 2012; 32(37): 12735–12743.

131. Scuderi C, Valenza M, Stecca C, et al. Palmitoylethanolamide exerts neuroprotective effects in mixed neuroglial cultures and organotypic hippocampal slices via peroxisome proliferator-activated receptor-alpha. *J Neuroinflammation* 2012; 9: 49.

132. Koch M, Kreutz S, Bottger C, et al. Palmitoylethanolamide protects dentate gyrus granule cells via peroxisome proliferator-activated receptor-alpha. *Neurotox Res* 2011; 19(2): 330–340.

133. Petrosino S, Schiano Moriello A, Verde R, et al. Palmitoylethanolamide counteracts substance P-induced mast cell activation in vitro by stimulating diacylglycerol lipase activity. *J Neuroinflammation* 2019; 16(1): 274.

134. Nam G, Jeong SK, Park BM, et al. Selective cannabinoid receptor-1 agonists regulate mast cell activation in an oxazolone-induced atopic dermatitis model. *Ann Dermatol* 2016; 28(1): 22–29.

135. Freitag CM and Miller RJ. Peroxisome proliferator-activated receptor agonists modulate neuropathic pain: a link to chemokines? *Front Cell Neurosci* 2014; 8: 238.

136. Paterniti I, Impellizzeri D, Crupi R, et al. Molecular evidence for the involvement of PPAR-delta and PPAR-gamma in anti-inflammatory and neuroprotective activities of palmitoylethanolamide after spinal cord trauma. *J Neuroinflammation* 2013; 10: 20.

137. Wallace VC, Segerdahl AR, Lambert DM, et al. The effect of the palmitoylethanolamide analogue, palmitoylallylamide (L-29) on pain behaviour in rodent models of neuropathy. *Br J Pharmacol* 2007; 151(7): 1117–1128.

138. Bettoni I, Comelli F, Colombo A, et al. Non-neuronal cell modulation relieves neuropathic pain: efficacy of the endogenous lipid palmitoylethanolamide. *CNS Neurol Disord Drug Targets* 2013; 12(1): 34–44.

139. Seol TK, Lee W, Park S, et al. Effect of palmitoylethanolamide on inflammatory and neuropathic pain in rats. *Korean J Anesthesiol* 2017; 70(5): 561–566.

140. Campolo M, Lanza M, Paterniti I, et al. PEA-OXA mitigates oxaliplatin-induced painful neuropathy through NF-kappaB/Nrf-2 axis. *Int J Mol Sci* 2021; 22(8): 3927.

141. Cristiano C, Avagliano C, Cuozzo M, et al. The beneficial effects of ultramicronized palmitoylethanolamide in the management of neuropathic pain and associated mood disorders induced by paclitaxel in mice. *Biomolecules* 2022; 12(8): 1155.

142. Elfarnawany A and Dehghani F. Palmitoylethanolamide mitigates paclitaxel toxicity in primary dorsal root ganglion neurons. *Biomolecules* 2022; 12(12): 1873.

143. Donvito G, Wilkerson JL, Damaj MI, et al. Palmitoylethanolamide reverses paclitaxel-induced allodynia in mice. *J Pharmacol Exp Ther* 2016; 359(2): 310–318.

144. Pickering E, Steels EL, Steadman KJ, et al. A randomized controlled trial assessing the safety and efficacy of palmitoylethanolamide for treating diabetic-related peripheral neuropathic pain. *Inflammopharmacology* 2022; 30(6): 2063–2077.

145. Schifilliti C, Cucinotta L, Fedele V, et al. Micronized palmitoylethanolamide reduces the symptoms of neuropathic pain in diabetic patients. *Pain Res Treat* 2014; 2014: 849623.

146. Zaiss M, Uhlig J, Zahn MO, et al. Improving chemotherapy-induced peripheral neuropathy in patients with breast or colon cancer after end of (neo)adjuvant therapy: results from the observational study STEFANO. *Oncol Res Treat* 2021; 44(11): 613–621.

147. Scuteri D, Guida F, Boccella S, et al. Effects of palmitoylethanolamide (PEA) on nociceptive, musculoskeletal and neuropathic pain: systematic review and meta-analysis of clinical evidence. *Pharmaceutics* 2022; 14(8): 1672.

148. Lang-Illievich K, Klivinyi C, Lasser C, et al. Palmitoylethanolamide in the treatment of chronic pain: a systematic review and meta-analysis of double-blind randomized controlled trials. *Nutrients* 2023; 15(6): 1350.

149. Artukoglu BB, Beyer C, Zuloff-Shani A, et al. Efficacy of palmitoylethanolamide for pain: a meta-analysis. *Pain Physician* 2017; 20(5): 353–362.

150. Paladini A, Fusco M, Cenacchi T, et al. Palmitoylethanolamide, a special food for medical purposes, in the treatment of chronic pain: a pooled data meta-analysis. *Pain Physician* 2016; 19(2): 11–24.

151. Deciga-Campos M, Jaramillo-Morales OA, Espinosa-Juarez JV, et al. N-palmitoylethanolamide synergizes the antinociception of morphine and gabapentin in the formalin test in mice. *J Pharm Pharmacol* 2023; 75(9): 1154–1162.

152. Di Cesare Mannelli L, Corti F, Micheli L, et al. Delay of morphine tolerance by palmitoylethanolamide. *Biomed Res Int* 2015; 2015: 894732.

153. Peritore AF, Siracusa R, Fusco R, et al. Ultramicronized palmitoylethanolamide and paracetamol, a new association to relieve hyperalgesia and pain in a sciatic nerve injury model in rat. *Int J Mol Sci* 2020; 21(10): 3509.

154. Steels E, Venkatesh R, Steels E, et al. A double-blind randomized placebo controlled study assessing safety, tolerability and efficacy of palmitoylethanolamide for symptoms of knee osteoarthritis. *Inflammopharmacology* 2019; 27(3): 475–485.

155. Nestmann ER. Safety of micronized palmitoylethanolamide (microPEA): lack of toxicity and genotoxic potential. *Food Sci Nutr* 2017; 5(2): 292–309.

156. De Gregorio D, Manchia M, Carpiniello B, et al. Role of palmitoylethanolamide (PEA) in depression: translational evidence: special section on "Translational and Neuroscience Studies in Affective Disorders." Section Editor, Maria Nobile MD, PhD. This Section of JAD focuses on the relevance of translational and neuroscience studies in providing a better understanding of the neural basis of affective disorders. The main aim is to briefly summaries relevant research findings in clinical neuroscience with particular regards to specific innovative topics in mood and anxiety disorders. *J Affect Disord* 2019; 255: S0165-0327(18)31599-4.

157. Coppola M and Mondola R. Is there a role for palmitoylethanolamide in the treatment of depression? *Med Hypotheses* 2014; 82(5): 507–511.

158. Merolla A, De Lorenzo R, Paolazzi G, et al. Micronized/ultramicronized

palmitoylethanolamide improves depression and fatigue in coronavirus disease 2019 (COVID-19) survivors. *Int Clin Psychopharmacol*. Epub ahead of print February 2024. DOI: 10.1097/YIC.0000000000000537.

159. Colizzi M, Bortoletto R, Costa R, et al. Palmitoylethanolamide and its biobehavioral correlates in autism spectrum disorder: a systematic review of human and animal evidence. *Nutrients* 2021; 13(4): 1346.
160. Khalaj M, Saghazadeh A, Shirazi E, et al. Palmitoylethanolamide as adjunctive therapy for autism: efficacy and safety results from a randomized controlled trial. *J Psychiatr Res* 2018; 103: 104–111.
161. Impellizzeri D, Bruschetta G, Cordaro M, et al. Micronized/ultramicronized palmitoylethanolamide displays superior oral efficacy compared to nonmicronized palmitoylethanolamide in a rat model of inflammatory pain. *J Neuroinflammation* 2014; 11: 136.
162. Gabrielsson L, Mattsson S and Fowler CJ. Palmitoylethanolamide for the treatment of pain: pharmacokinetics, safety and efficacy. *Br J Clin Pharmacol* 2016; 82(4): 932–942.
163. Houston MC. Clonidine hydrochloride: review of pharmacologic and clinical aspects. *Prog Cardiovasc Dis* 1981; 23(5): 337–350.
164. Neuchat EE, Bocklud BE, Kingsley K, et al. The role of alpha-2 agonists for attention deficit hyperactivity disorder in children: a review. *Neurol Int* 2023; 15(2): 697–707.
165. Farhat LC, Behling E, Landeros-Weisenberger A, et al. Comparative efficacy, tolerability, and acceptability of pharmacological interventions for the treatment of children, adolescents, and young adults with Tourette's syndrome: a systematic review and network meta-analysis. *Lancet Child Adolesc Health* 2023; 7(2): 112–126.
166. Hassanzadeh S, Bagheri S, Majid Ahmadi S, et al. Effectiveness of oral clonidine and gabapentin on peripheral neuropathy in diabetic patients in southwestern Iran: a randomized clinical trial. *BMC Endocr Disord* 2023; 23(1): 224.
167. Serednicki WT, Wrzosek A, Woron J, et al. Topical clonidine for neuropathic pain in adults. *Cochrane Database Syst Rev* 2022; 5(5): CD010967.
168. Fulas OA, Laferriere A, Ware DMA, et al. The effect of a topical combination of clonidine and pentoxifylline on post-traumatic neuropathic pain patients: study protocol for a randomized, double-blind placebo-controlled trial. *Trials* 2021; 22(1): 149.
169. Yoon SY, Roh DH, Yeo JH, et al. Analgesic efficacy of alpha(2) adrenergic receptor agonists depends on the chronic state of neuropathic pain: role of regulator of G protein signaling 4. *Neuroscience* 2021; 455: 177–194.
170. Ydemann M, Nielsen BN, Henneberg S, et al. Intraoperative clonidine for prevention of postoperative agitation in children anaesthetised with sevoflurane (PREVENT AGITATION): a randomised, placebo-controlled, double-blind trial. *Lancet Child Adolesc Health* 2018; 2(1): 15–24.
171. Taghizadeh N and Davidson A. Does clonidine premedication decrease postoperative pain in children? *J Paediatr Child Health* 2016; 52(1): 93–94.
172. Shukla U, Prabhakar T and Malhotra K. Postoperative analgesia in children when using clonidine or fentanyl with ropivacaine given caudally. *J Anaesthesiol Clin Pharmacol* 2011; 27(2): 205–210.
173. Schmidt AP, Valinetti EA, Bandeira D, et al. Effects of preanesthetic administration of midazolam, clonidine, or dexmedetomidine on postoperative pain and anxiety in children. *Paediatr Anaesth* 2007; 17(7): 667–674.
174. Reimer EJ, Dunn GS, Montgomery CJ, et al. The effectiveness of clonidine as an analgesic in paediatric adenotonsillectomy. *Can J Anaesth* 1998; 45(12): 1162–1167.
175. Nishina K and Mikawa K. Clonidine in paediatric anaesthesia. *Curr Opin Anaesthesiol* 2002; 15(3): 309–316.
176. Mikawa K, Nishina K, Maekawa N, et al. Oral clonidine premedication reduces postoperative pain in children. *Anesth Analg* 1996; 82(2): 225–230.
177. Mikawa K, Nishina K, Maekawa N, et al. Oral clonidine premedication reduces vomiting in children after strabismus surgery. *Can J Anaesth* 1995; 42(11): 977–981.
178. Bousquet P. Imidazoline receptors: from basic concepts to recent developments. *J Cardiovasc Pharmacol* 1995; 26(Suppl 2): S1–S6.
179. Fairbanks CA, Stone LS, Kitto KF, et al. alpha(2C)-Adrenergic receptors mediate spinal analgesia and adrenergic-opioid synergy. *J Pharmacol Exp Ther* 2002; 300(1): 282–290.
180. Sanchez-Blazquez P, Boronat MA, Olmos G, et al. Activation of I(2)-imidazoline receptors enhances supraspinal morphine analgesia in

mice: a model to detect agonist and antagonist activities at these receptors. *Br J Pharmacol* 2000; 130(1): 146–152.

181. Khan ZP, Ferguson CN and Jones RM. alpha-2 and imidazoline receptor agonists. Their pharmacology and therapeutic role. *Anaesthesia* 1999; 54(2): 146–165.

182. Tanaka T and Starke K. Antagonist/agonist-preferring alpha-adrenoceptors or alpha 1/alpha 2-adrenoceptors? *Eur J Pharmacol* 1980; 63(2–3): 191–194.

183. Coupry I, Lachaud V, Podevin RA, et al. Different affinities of alpha 2-agonists for imidazoline and alpha 2-adrenergic receptors. *Am J Hypertens* 1989; 2(6 Pt 1): 468–470.

184. Offermeier J, van Rooyen JM and Rossouw J. The alpha 1- and alpha 2-adrenoceptor selectivity of drugs with potential effects on blood pressure—a radioligand-binding study. *S Afr Med J* 1986; 69(4): 234–236.

185. Giovannitti JA Jr, Thoms SM and Crawford JJ. Alpha-2 adrenergic receptor agonists: a review of current clinical applications. *Anesth Prog* 2015; 62(1): 31–39.

186. Howe JR, Wang JY and Yaksh TL. Selective antagonism of the antinociceptive effect of intrathecally applied alpha adrenergic agonists by intrathecal prazosin and intrathecal yohimbine. *J Pharmacol Exp Ther* 1983; 224(3): 552–558.

187. Kuraishi Y, Hirota N, Sato Y, et al. Noradrenergic inhibition of the release of substance P from the primary afferents in the rabbit spinal dorsal horn. *Brain Res* 1985; 359(1–2): 177–182.

188. Zhang JM, Song XJ and LaMotte RH. An in vitro study of ectopic discharge generation and adrenergic sensitivity in the intact, nerve-injured rat dorsal root ganglion. *Pain* 1997; 72(1–2): 51–57.

189. Duflo F, Li X, Bantel C, et al. Peripheral nerve injury alters the alpha2 adrenoceptor subtype activated by clonidine for analgesia. *Anesthesiology* 2002; 97(3): 636–641.

190. Khasar SG, Green PG, Chou B, et al. Peripheral nociceptive effects of alpha 2-adrenergic receptor agonists in the rat. *Neuroscience* 1995; 66(2): 427–432.

191. Hayashida KI, Clayton BA, Johnson JE, et al. Brain derived nerve growth factor induces spinal noradrenergic fiber sprouting and enhances clonidine analgesia following nerve injury in rats. *Pain* 2008; 136(3): 348–355.

192. Lavand'homme PM, Ma W, De Kock M, et al. Perineural alpha(2A)-adrenoceptor activation inhibits spinal cord neuroplasticity and tactile allodynia after nerve injury. *Anesthesiology* 2002; 97(4): 972–980.

193. Pohjanoksa K, Jansson CC, Luomala K, et al. Alpha2-adrenoceptor regulation of adenylyl cyclase in CHO cells: dependence on receptor density, receptor subtype and current activity of adenylyl cyclase. *Eur J Pharmacol* 1997; 335(1): 53–63.

194. Lepretre N and Mironneau J. Alpha 2-adrenoceptors activate dihydropyridine-sensitive calcium channels via Gi-proteins and protein kinase C in rat portal vein myocytes. *Pflugers Arch* 1994; 429(2): 253–261.

195. Sanchez-Blazquez P and Garzon J. Further characterization of alpha N-acetyl beta-endorphin-(1-31) regulatory activity, I: effect on opioid- and alpha 2-mediated supraspinal antinociception in mice. *Life Sci* 1992; 50(26): 2083–2097.

196. Chakraborty S, Elvezio V, Kaczocha M, et al. Presynaptic inhibition of transient receptor potential vanilloid type 1 (TRPV1) receptors by noradrenaline in nociceptive neurons. *J Physiol* 2017; 595(8): 2639–2660.

197. Longhitano L, Distefano A, Murabito P, et al. Propofol and alpha2-agonists attenuate microglia activation and restore mitochondrial function in an in vitro model of microglia hypoxia/reoxygenation. *Antioxidants (Basel)* 2022; 11(9): 1346.

198. Novak-Jankovic V, Paver-Eržen V, Bovill JG, et al. Effect of epidural and intravenous clonidine on the neuro-endocrine and immune stress response in patients undergoing lung surgery. *Eur J Anaesthesiol* 2000; 17(1): 50–56.

199. Walker SM, Grafe M and Yaksh TL. Intrathecal clonidine in the neonatal rat: dose-dependent analgesia and evaluation of spinal apoptosis and toxicity. *Anesth Analg* 2012; 115(2): 450–460.

200. Zhang F, Feng X, Dong R, et al. Effects of clonidine on bilateral pain behaviors and inflammatory response in rats under the state of neuropathic pain. *Neurosci Lett* 2011; 505(3): 254–259.

201. Bhalla S, Andurkar SV and Gulati A. Involvement of alpha(2)-adrenoceptors, imidazoline, and endothelin—a receptors in the effect of agmatine on morphine and oxycodone-induced hypothermia in mice. *Fundam Clin Pharmacol* 2013; 27(5): 498–509.

202. Andurkar SV, Gendler L and Gulati A. Tramadol antinociception is potentiated by clonidine through alpha(2)-adrenergic and I(2)-imidazoline but not by endothelin ET(A) receptors in mice. *Eur J Pharmacol* 2012; 683(1–3): 109–115.

203. Siemian JN, Obeng S, Zhang Y, et al. Antinociceptive interactions between the imidazoline I2 receptor agonist 2-BFI and opioids in rats: role of efficacy at the mu-opioid receptor. *J Pharmacol Exp Ther* 2016; 357(3): 509–519.

204. Stone LS, German JP, Kitto KF, et al. Morphine and clonidine combination therapy improves therapeutic window in mice: synergy in antinociceptive but not in sedative or cardiovascular effects. *PLoS One* 2014; 9(10):e109903.

205. Siemian JN, Li J, Zhang Y, et al. Interactions between imidazoline I2 receptor ligands and acetaminophen in adult male rats: antinociception and schedule-controlled responding. *Psychopharmacology (Berl)* 2016; 233(5): 873–882.

206. Inomata S, Kakiuchi Y, Miyabe M, et al. Combined therapy with clonidine and amantadine may act in two stages of glutamate-mediated neuropathic pain caused by a needle puncture in an upper extremity. *Anesth Analg* 2005; 101(3): 921–922.

207. Baker AK, Hoffmann VL and Meert TF. Interactions of NMDA antagonists and an alpha 2 agonist with mu, delta and kappa opioids in an acute nociception assay. *Acta Anaesthesiol Belg* 2002; 53(3): 203–212.

208. Bailey PL, Sperry RJ, Johnson GK, et al. Respiratory effects of clonidine alone and combined with morphine, in humans. *Anesthesiology* 1991; 74(1): 43–48.

209. Jarvis DA, Duncan SR, Segal IS, et al. Ventilatory effects of clonidine alone and in the presence of alfentanil, in human volunteers. *Anesthesiology* 1992; 76(6): 899–905.

210. Yeo JH, Yoon SY, Kim SJ, et al. Clonidine, an alpha-2 adrenoceptor agonist relieves mechanical allodynia in oxaliplatin-induced neuropathic mice; potentiation by spinal p38 MAPK inhibition without motor dysfunction and hypotension. *Int J Cancer* 2016; 138(10): 2466–2476.

211. Choi S, Yamada A, Kim W, et al. Noradrenergic inhibition of spinal hyperexcitation elicited by cutaneous cold stimuli in rats with oxaliplatin-induced allodynia: electrophysiological and behavioral assessments. *J Physiol Sci* 2017; 67(3): 431–438.

212. Lynch JJ 3rd, Wade CL, Zhong CM, et al. Attenuation of mechanical allodynia by clinically utilized drugs in a rat chemotherapy-induced neuropathic pain model. *Pain* 2004; 110(1–2): 56–63.

213. Costa-Pereira JT, Ribeiro J, Martins I, et al. Role of spinal cord alpha(2)-adrenoreceptors in noradrenergic inhibition of nociceptive transmission during chemotherapy-induced peripheral neuropathy. *Front Neurosci* 2019; 13: 1413.

214. Bamgbade OA, Tai-Osagbemi J, Bamgbade DO, et al. Clonidine is better than zopiclone for insomnia treatment in chronic pain patients. *J Clin Sleep Med* 2022; 18(6): 1565–1571.

215. Zeigler D, Lynch SA, Muir J, et al. Transdermal clonidine versus placebo in painful diabetic neuropathy. *Pain* 1992; 48(3): 403–408.

216. Byas-Smith MG, Max MB, Muir J, et al. Transdermal clonidine compared to placebo in painful diabetic neuropathy using a two-stage "enriched enrollment" design. *Pain* 1995; 60(3): 267–274.

217. Crispin H and Banting M. Intravenous clonidine infusion for refractory pain and agitation in central nervous system leukaemia. *BMJ Support Palliat Care* 2024; 13(e3): e774–e775.

218. Howard P, Clawson S and Curtin J. Short subcutaneous infusions for symptom control in palliative medicine. *BMJ Support Palliat Care* 2024; 14(2): 183–186.

219. Neil MJ. Clonidine: clinical pharmacology and therapeutic use in pain management. *Curr Clin Pharmacol* 2011; 6(4): 280–287.

220. Burris JF. The USA experience with the clonidine transdermal therapeutic system. *Clin Auton Res* 1993; 3(6): 391–396.