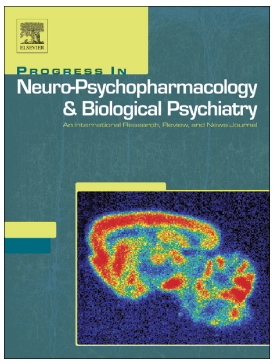

Overlaps in pharmacology for the treatment of chronic pain and mental health disorders

Ainsley M. Sutherland, Judith Nicholls, James Bao, Hance Clarke

PII: S0278-5846(17)30382-2
DOI: doi:10.1016/j.pnpbp.2018.07.017
Reference: PNP 9452

To appear in: *Progress in Neuropsychopharmacology & Biological Psychiatry*

Received date: 14 May 2017
Revised date: 13 July 2018
Accepted date: 18 July 2018

Please cite this article as: Ainsley M. Sutherland, Judith Nicholls, James Bao, Hance Clarke , Overlaps in pharmacology for the treatment of chronic pain and mental health disorders. Pnp (2018), doi:10.1016/j.pnpbp.2018.07.017

Overlaps in Pharmacology for the Treatment of Chronic pain and Mental Health Disorders

Ainsley M. Sutherland, MD, PhD[3]; Judith Nicholls, MD[1]; James Bao, MSPH[1], Hance Clarke, MD, PhD[1,2]

1. Pain Research Unit, Department of Anesthesia and Pain Medicine, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada, M5G 2C4

2. Department of Anesthesia, University of Toronto, Toronto, Ontario, Canada

3. Department of Anesthesia, University of British Columbia, Vancouver, British Columbia

Corresponding Author: Dr. Hance Clarke, Staff Anesthesiologist, Director of Clinical Pain Services and Medical Director of Pain Research Unit, Toronto General Hospital, 200 Elizabeth Street, Toronto, ON Canada. E-mail: Hance.Clarke@uhn.ca phone: 416-340-4800 ext 2927 fax: 416-340-3698

Abstract

There is significant overlap in the pharmacological management of pain and psychological disorders. Appropriate treatment of patients' comorbid psychological disorders, including sleep disturbances often leads to an improvement in reported pain intensity. The three first line agents for neuropathic pain include tricyclic antidepressants and serotonin norepinephrine reuptake inhibitors which are medications originally developed as antidepressants. The other first line medication for chronic neuropathic pain are anticonvulsant medications initially brought to the market-place for the treatment of epilepsy and are also now being used for the treatment of anxiety disorders and substance withdrawal symptoms. The efficacy of opioids for chronic pain is contentious, but it is agreed that the patients at highest risk for opioid misuse and addiction are patients with underlying psychological disorders who use opioids for their euphoric effects. Similarly, benzodiazepines may present a problem in patients with chronic pain, as up to one third of patients with pain are concomitantly prescribed benzodiazepines, and when combined with other sedating analgesic medications they put patients at increased risk for adverse events and polysubstance misuse. Finally, there is growing evidence for the efficacy of cannabis for treating neuropathic pain, but the consumption of cannabis has been associated with increased risk of psychosis in adolescents, and may be associated with an increased risk for developing bipolar disorder and anxiety disorders. The use of cannabis is associated with an increased risk of substance misuse in both adolescents and adults. In this narrative review, we examine the evidence for the use of several medications used for the treatment of both pain and psychological disorders, and their proposed mechanisms of action, in addition to special concerns for patients with comorbid pain and psychological disorders.

Introduction

Many patients presenting to chronic pain clinics with chronic pain syndromes have comorbid psychological disorders. Addressing these psychological illnesses is integral to achieving successful chronic pain management outcomes. Treating comorbid psychological illnesses such as anxiety and depression will have a positive effect on pain, and on the patient's ability to manage their pain and reduce opioid consumption (1). Likewise, adequate management of a patient's pain will improve sleep, energy and mood (2, 3). Central and peripheral noradrenergic pathways play a key role in both pain and mood disorders, and it is for this reason that many first line treatments for chronic pain - particularly neuropathic pain - were originally developed as antidepressants.

Patients with comorbid psychological and pain disorders are at increased risk of misusing opioids and benzodiazepines to treat both their emotional and physical pain (4-8) (9). Identification of these patients and working with them to develop more adaptive strategies for coping with their pain, including pharmacotherapy with medications with less abuse potential, can lessen the risk of serious complications of their substance use disorder (10).

Earlier in this special issue, comorbid pain and psychiatric illnesses were reviewed. In this narrative review we will discuss the overlap of pharmacotherapy for pain and psychiatric disorders, including the concomitant use of opioids and benzodiazepines in chronic pain patients who are at high risk of substance use disorders.

Overlapping Pharmacotherapy for Pain and Psychological Disorders

Antidepressants

Tricyclic antidepressants (TCAs) were first noted to be effective analgesics for neuropathic pain in patients being treated for depression with imipramine (11). TCAs act primarily by inhibiting synaptic reuptake of serotonin (5-HT) and norepinephrine (NE) (12). They also have effects at 5-HT, a-1 adrenergic, histamine (H1 and H2) and N-methyl-D-aspartate (NMDA) receptor antagonists (13-15), which do not play a role in analgesia, and contribute to their unfavourable side effect profile. Preclinical studies have also suggested that TCAs, particularly amitriptyline, may be a functional inhibitor of NMDA receptor activation, however, this is not felt to be the mechanism through which TCAs exert their analgesic effect, as this would result in more rapid analgesia than is seen clinically (16). Since then numerous studies have demonstrated efficacy of TCAs and newer 5-HT and NE reuptake inhibitors (SNRIs) for analgesia in neuropathic pain, and while recent systematic reviews seem to favour duloxetine over amitriptyline or nortriptyline, decades of therapy with amitriptyline have demonstrated its efficacy in the treatment of neuropathic pain (17-19). Accordingly, TCAs and SNRIs are considered first line for neuropathic pain, along with gabapentenoids (20-23). TCAs have largely fallen out of favour for the treatment of mood disorders because of their anticholinergic adverse effects and their predisposition to cause adverse cardiac effects (24). Specifically, TCAs have been purported to induce cardiac Na+ channel blockade, manifesting in prolonged PR, QRS and QT intervals as well as orthostatic hypotension. In either patients with pre-existing conduction defects or in cases of overdose, the prolonged conduction effects may lead to heart block or arrhythmias (25). The analgesic effect of these antidepressants takes several days to weeks to occur and is thought to

be mediated through molecular and neural plasticity mechanisms, as for depression (26). However, attenuation of allodynia and hyperalgesia is typically achieved more rapidly and with lower doses than those required for depression (27, 28) (see Table 1).

Preclinical animal studies indicate that it is the noradrenergic, rather than the serotonergic, effects of these antidepressant medications that are responsible for long-term pain relief. In fact, studies using a selective NE reuptake inhibitor (reboxetine) demonstrated good analgesic effect (29), while studies of selective 5-HT reuptake inhibitors (SSRIs) in both rat models of neuropathic pain and in clinical trials show limited effects (27). Intrathecal injection of serotonin or a 5HT3 antagonist did, however, inhibit allodynia in a rat model of neuropathic pain and rat models of SSRIs in pain indicate that they may have nociceptive analgesic effects (30). Serotonin thus may play a modulating, synergistic role with noradrenaline in the treatment of neuropathic pain with TCAs and SNRIs (22, 27) through spinal 5-HT3 receptors in the dorsal horn (31).

The anti-allodynic effects of long-term TCA or SNRI therapy is thought to be mediated through the recruitment of α2- and β2-adrenoreceptors in noradrenergic descending pathways of afferent pain signalling in the spinal cord, and through potentiation of descending inhibition mediated by neurons of the rostroventral medulla (27). This results in a decrease in nociceptive transmission in the ascending spinal pain pathways.

TCAs and SNRIs may also decrease levels of pro-inflammatory cytokines (ie. tumor necrosis factor alpha [TNFα], interleukin-6 [IL6], IL-1 beta [IL-1β]) involved in the process known as neurogenic inflammation (32-34). Nociceptors on Aδ and C fibres located in skin, muscle, bone and connective tissue respond to high intensity stimuli and transduce the physical energy into action potentials which are transmitted along the neuron to the cell bodies in the DRG and on to the central nervous system (CNS) (35). Activation of nociceptors is modulated by the local inflammatory and chemical extracellular environment (36). Nociceptors release polypeptide mediators such as Substance P from their peripheral nerve endings into surrounding tissue causing degranulation of mast cells and activation of immune cells (37, 38). Substance P also causes vasodilation through the induction of endothelial nitric oxide synthase (eNOS) and subsequent production of nitric oxide (37, 38). In rat models of neuropathic pain, pro-inflammatory cytokine levels have been demonstrated to increase following nerve injury. In particular, sites of nerve damage demonstrate pro-inflammatory cytokine release of TNFα, which induces activity in injured and uninjured afferent nociceptors (39, 40). Tricyclic antidepressants (nortriptyline), SNRIs (venlafaxine), and mirtazapine, have been shown to subsequently decrease levels of TNFα, possibly through a β2-adrenoreceptor-mediated mechanism (32-34).

The anti-allodynic effects of TCA and SNRI therapy require an intact opioid system and may work by increasing the production of opioid peptides such as enkephalins and β-endorphins, and/or the expression of μ-opioid and δ-opioid receptors in the spinal cord (27). In murine models of neuropathic pain, mice that were deficient in δ-opioid receptors did not derive anti-

allodynic benefit from chronic nortriptyline treatment (41, 42). The effects of antidepressants on the opioid system may again be mediated through the adrenergic system.

Tricyclic Antidepressants

TCAs have been shown in small studies to be effective in the treatment of painful diabetic neuropathy (PDN), post-herpetic neuralgia (PHN) and central pain. This analgesic effect is seen whether the patient is depressed or not, and analgesia does not correlate with resolution of depression (43, 44). Amitriptyline and nortriptyline are the most widely prescribed TCAs for neuropathic pain. Nortriptyline is an active metabolite of amitriptyline. Analgesia takes days to weeks of treatment at doses of 25-150 mg per day (17, 19, 26). The most recent Cochrane reviews of TCAs for neuropathic pain calculate a number needed to treat (NNT) for amitriptyline in the neuropathic pain conditions of PDN, PHN, and mixed neuropathic pain of 5.1 (95% CI 3.5 - 9.3) (19). The authors state that this is probably an overestimation of the efficacy of amitriptyline as most of the studies included in the meta-analysis were of poor to moderate quality and subject to bias due to small sample size and short duration (19). A separate Cochrane review of nortriptyline for neuropathic pain found little evidence to support the use of nortriptyline to treat neuropathic pain (17), although this is in part due to the fact that the majority of studies of TCAs in neuropathic pain were done with amitriptyline. A NNT for nortriptyline in neuropathic pain conditions could not be calculated as there were only 6 studies of poor quality in different pain conditions, so data could not be pooled (17). The authors concluded that nortriptyline should not be considered as a first line agent for neuropathic pain (17). Similarly, a recent systematic review found little supporting evidence for

using imipramine to treat neuropathic pain (45). No numbers needed to harm (NNH) for amitriptyline, nortriptyline or imipramine were calculated in the more recent systematic reviews, but an earlier Cochrane review of TCAs in neuropathic pain stated a NNH of 6 for all TCAs (95% CI 4.2-10.7) was found (28).

TCAs should be avoided in patients with cardiovascular comorbidities, or who are at risk of overdose as they are one of the commonest causes of drug poisoning and have high rates of fatality. Less serious side effects to warn patients about include drowsiness, dizziness, dry mouth, nausea, weight gain and urinary retention (19). Amitriptyline is normally administered at night to avoid daytime sedation.

Serotonin and norepinephrine reuptake inhibitors

The serotonin and norepinephrine reuptake inhibitors (SNRIs) venlafaxine, desvenlafaxine and duloxetine have been shown to be effective in treating neuropathic pain in a number of clinical trials and are considered to be first line treatment for neuropathic pain conditions along with TCAs and gabapentinoids (20-23). In psychiatric practice, they are indicated for major depressive disorder and generalized anxiety disorder. Venlafaxine is also used off-label for post-traumatic stress disorder (PTSD) (46). The analgesic effect of SNRIs are independent of their effect on mood (44).

The strongest evidence for duloxetine is in treating PDN and fibromyalgia. In a recent systematic review of 8 studies in PDN, duloxetine at 60 mg was found to have a NNT for a 50%

reduction in pain of 5 (95% CI 4 to 7) (18). The NNT for a 50% pain reduction based on 6 studies of fibromyalgia is 8 (95% CI 4 to 21) at a dose of 60 mg daily (18). A dose of 120 mg daily was no more effective in PDN or fibromyalgia than 60 mg. Duloxetine was not found to be effective in treating central neuropathic pain resulting from a stroke or spinal cord injury, although there has only been a single small trial examining this (47). 12.6% of patients in these studies stopped using duloxetine because of side effects. Adverse effects were common, but rarely serious, and included sedation, nausea, constipation, headache, dry mouth and dizziness (18). The NNH of duloxetine 60 mg daily for all neuropathic pain conditions was calculated to be 18 (95% CI 13 to 30) (18).

There is some evidence for duloxetine in other pain syndromes. A five-week course of duloxetine 60 mg daily was found to decrease pain from chemotherapy induced neuropathy relative to placebo (48). However, patients treated with duloxetine had only a mean decrease in average pain scores of 1.06 on the visual analogue scale (VAS), so the clinical meaningfulness has been questioned (48). A 12-week double-blind, randomized control trial of duloxetine 60 mg daily versus placebo in 401 patients with non-neuropathic chronic low back pain (CLBP) demonstrated a significantly greater reduction in the Brief Pain Inventory (BPI) average pain in patients treated with duloxetine (49). 15.2% of the patients treated with duloxetine (vs. 5.4% of patients treated with placebo) dropped out of the study because of side effects (49). A follow up study of patients who had at least a 30% reduction in BPI average pain at the end of the placebo-controlled trial, and placebo patients who were switched to duloxetine at the end of the trial (n=181), demonstrated ongoing further significant improvements in pain, physical

function, and quality of life (50). Duloxetine has also been suggested to be efficacious in patients with CLBP with radiculopathy. A small randomized, placebo-controlled, double-blind crossover trial of 41 patients with chronic low back pain with a neuropathic component found that VAS scores were lower in the duloxetine phase compared with placebo (4.1 ± 2.9 vs. 6.0 ± 2.7; P = 0.001) (51). While intriguing, only 21 patients completed the study, and patients only received duloxetine for 4 weeks (51). Further study is warranted.

There is stronger evidence for the use of duloxetine in chronic osteoarthritis (OA) knee pain. A systematic review of three RCTs that included 1011 patients with knee OA demonstrated that duloxetine 60 or 120 mg daily resulted in a significantly greater number of patients reporting a >30% or >50% reduction in pain, improved function and patient-rated impression of improvement after 10-13 weeks of treatment versus placebo (52).

Venlafaxine is less commonly prescribed than duloxetine for pain, and there is less compelling evidence for its use (53). A meta-analysis of six RCTs of venlafaxine 50 – 225 mg daily in neuropathic pain that included 4 crossover trials demonstrated benefit of the drug in neuropathic pain. Most of the patients enrolled in the studies had PDN, so it is unclear what benefit venlafaxine may provide in other pain syndromes, and all studies were subject to significant bias due to small sample size and short duration, so the benefit may be overstated (53). The authors concluded that there was no reason to change current neuropathic pain guidelines (20-23) in favour of venlafaxine.

Desvenlafaxine has been examined for use in fibromyalgia and PDN in two industry-sponsored trials (54, 55). In a multicentre, randomized, placebo-controlled study, desvenlafaxine was not found to be efficacious in treating symptoms of fibromyalgia, and in fact the trial was stopped early because of lack of efficacy versus placebo (55). In a randomized, double-blind, placebo-controlled trial of desvenlafaxine at doses of 50, 100, 200 or 400 mg daily versus placebo for PDN, doses of 200 and 400 mg per day were found to be effective at relieving pain from PDN after 13 weeks of treatment (54). Lower doses of 50 and 100 mg per day were not found to be superior to placebo for pain relief. Nausea and dizziness were the most commonly reported side effects (54). Given the limited data of the effectiveness of desvenlafaxine for the treatment of pain, it should not be used before a trial of duloxetine or a TCA.

Gabapentinoids

The anticonvulsants gabapentin and pregabalin are considered first line agents for neuropathic pain (20, 22, 23). These medications have been advocated for use in patients with comorbid anxiety, depression and chronic pain in combination with TCAs or duloxetine (56). Gabapentin may be effective in generalized anxiety disorder with comorbid substance use disorder, and social anxiety disorder that does not respond to first line treatments (57, 58). Pregabalin has also been shown to be efficacious and cost-effective in the treatment of generalized anxiety disorder (59). There is good evidence for the use of gabapentin in treating symptoms of mild alcohol withdrawal during detoxification (60).

Gabapentin and pregabalin bind the $\alpha_2\delta$ subunit of voltage-gated calcium channels (61, 62), and their antinociceptive effects are thought to be mediated through modulation of calcium influx into cells (63, 64). $\alpha_2\delta$ subunits have been shown to have increased expression in animal models of neuropathic pain (65, 66). Gabapentinoids also modulate downstream overexpression of pro-inflammatory cytokines. TNF-α at the dorsal root ganglia has been shown to be suppressed by pregabalin treatment (27). In the spinal cord, elevated levels of inflammatory cytokines including TNFα, IL-6 and IL-1B have been shown to be inhibited with intrathecal administration of gabapentin, likely through increased expression of the anti-inflammatory cytokine IL-10 (67). Several other mechanisms for gabapentinoids have been proposed, including selective enhancement of the NMDA current at GABA interneurons, activation of ATP-sensitive K+ channels, and blockade of AMPA-receptor mediated transmission (68). However, $\alpha_2\delta$ remains the most likely molecular target for gabapentinoid's analgesic actions (69). Repeated treatment with gabapentin or pregabalin has been shown to normalize spinal $\alpha_2\delta$ subunit levels at DRG presynaptic terminals (70, 71). Gabapentin and pregabalin inhibit hyperactivity and central sensitization of dorsal horn neurons in models of neuropathic pain, possibly through inhibition of release of aspartate and glutamate (72).

A Cochrane systematic review of 37 studies of gabapentin in PDN, PHN or mixed neuropathic pain found that oral gabapentin lead to a 50% reduction in pain in PHN (risk ratio (RR) 1.69 [1.43, 2.00], and PDN (RR 1.86[1.53,2.27]) (73, 74). A dose of at least 1200mg daily was required for effect (400mg TID). The NNT for PHN and PDN were between 5 and 7 for substantial and at least moderate improvement in symptoms (73). A single study of gabapentin

in fibromyalgia determined that it provided at least moderate improvement in symptoms (RR 1.61 [1.07, 2.42]) at a dose of 2400mg daily (75). The review determined that there was no strong evidence of efficacy for gabapentin in trigeminal neuralgia, postoperative or traumatic neuropathic pain, HIV-neuropathy, spinal cord injury, complex regional pain syndrome type 1 (CRPS-1), or masticatory myalgia (73). The most common adverse effects were dizziness (19% with doses > 1200mg/day), sedation (14% with doses > 1200mg/day), peripheral edema (7%), ataxia or gait disturbance (8.8%) (73).

Pregabalin has similarly been found to be effective for PHN, and PDN, with somewhat less efficacy for central pain and fibromyalgia (76), and no efficacy for HIV-neuropathy (22), as defined by at least 30% pain relief over baseline, improved patient global impression of change, or lack of efficacy discontinuation (76). A dose-response has been demonstrated, with 600mg daily being more effective than 300mg daily. The NNT for various neuropathic pain conditions were found to be 3.9 (95% CI 3.1-5.1) for PHN, 5.0 (95% CI 4.0-6.6) for PDN, 5.6 (95% CI 3.5-14) for central neuropathic pain, and 11 (95% CI 7.1-21) for fibromyalgia (76). The side effect profile is similar to that of gabapentin with 15-25% of patients taking 600mg daily complaining of somnolence and 27% to 46% complaining of dizziness (76).

Opioids

Nociceptive pain is modulated both peripherally by the local extracellular inflammatory environment, and centrally by descending pain-modulating pathways that act on the dorsal horn to control nociceptive transmission to the cortex. Neurons of the efferent nociceptive

pathway travel via the raphespinal tract and reticulospinal tract to the dorsal horn where they modulate nociception via enkephalinergic neurons that act on second-order nociceptive neurons (77-79). Enkephalinergic neurons release the endogenous opioids enkaphelin and α-endorphins that regulate and inhibit nociceptive stimuli.

Opioids are not a psychiatric medication, however, patients with psychological disorders can misuse them for their euphoric effects. Potent exogenous opioids, including morphine and its synthetic derivatives hydromorphone, oxycodone, and fentanyl, act primarily as μ1 and μ2 opioid receptor agonists at pre- and post-synaptic sites in the brainstem and primary afferent and interneurons of the spinal cord (80, 81). Opioid receptors have also been demonstrated on immune cells and sensory neurons in the periphery (82). These drugs mimic the actions of endogenous opioid agonists – enkephalins, endorphins, and dynorphins – to inhibit presynaptic release of neurotransmitters (acetylcholine [ACh], dopamine [DA], NE, substance P) and inhibit transmission of nociceptive stimuli (80-82). The μ1 receptor is thought to be responsible for feelings of euphoria with opioid administration (83), while activation of the μ2 receptor is thought to lead to physical dependence. Binding of opioid medications with μ-opioid receptors often results in analgesia and possibly euphoria, with significant risk of side effects such as respiratory depression, overdose, constipation, urinary retention, physical dependence and addiction (84). The kappa receptor is thought to be responsible for spinal analgesia, sedation, dyspnea and respiratory depression, and is found in the limbic system, brain stem and spinal cord. Delta opioid receptors are located in the brain and may be associated with dysphoric and psychomimetic effects (83). All opioid receptors are coupled to inhibitory G-proteins to exert

their intra-cellular effects. These include K+ efflux leading to hyperpolarization, inhibition of adenylyl cyclase leading to reduced cAMP and closing of voltage sensitive calcium channels. This ultimately decreases excitability of neurons and subsequently inhibits downstream neurotransmitter release (85). While opioids are effective first-line agents for management of severe, acute pain, their role in management of chronic pain has been called into question because of the side effects and the risk of substance misuse, particularly in patients with psychological disorders. Repeated use of opioids can also lead to a paradoxical opioid-induced hyperalgesia, that leads to increased dosage requirements and worsening pain. Sustained opioid use also facilitates tolerance, which may eventually require escalating doses to maintain sufficient pain management (86).

Rates of opioid misuse in patients with chronic pain have been found to be between 21% and 29% (95% CI 13%-38%) and rates of addiction between 8% and 12% (95% CI 3%-17%) (87). Other Cochrane reviews identify the rates of addiction in well managed chronic pain patients to be less than 1% (88). Definitions of misuse included underuse or overuse, erratic use, inappropriate use (ie. for managing symptoms of anxiety or other distress), and concurrent use with other substances (87). Serious mental illness including major depressive disorder and post-traumatic stress disorder have been consistently associated with higher rates of misuse of and addiction to prescription opioids (4-8). In the 2002-2004 National Survey on Drug Use and Health non-medical use of prescription opioids in the past year was associated with panic, depressive and social phobic/agoraphobic symptoms, and patients with these symptoms were more likely to meet the criteria for opioid abuse/dependence (4). An Axis I or II diagnosis is

associated with an increased likelihood of developing an opioid use disorder (7, 8). It is therefore important to screen patients for symptoms of anxiety and depression, and to be aware of psychiatric diagnoses in order to identify patients who may be at increased risk for developing an opioid use disorder and ensure monitoring of opioid prescriptions and specialist care for the psychological condition.

While managing chronic pain patients with opioids it is also important to keep in mind that patients who demonstrate aberrant drug-seeking behaviours may meet the criteria for opioid use disorder, or they may be misusing opioids because of uncontrolled pain, anxiety or fear of withdrawal (89, 90). A thorough history and discussion with patients around their opioid use, cravings and withdrawal symptoms is key to establishing a diagnosis. Education as to appropriate use and timing of opioid medications may also positively change behaviour (89, 90).

Weak opioids with SNRI antidepressant effects such as tramadol and tapentadol may have some efficacy in neuropathic pain. Codeine is another weak opioid, but lacks the antidepressant effects of tramadol and tapentadol. Tramadol is a weak synthetic opioid that acts as an agonist at the μ-opioid receptor, and also as a 5-HT and NE reuptake inhibitor (91). It is increasingly being prescribed as an alternative to high potency opioids with the belief that it may less prone to abuse, and patients may benefit from its antidepressant effects. The lower risk of abuse is controversial as recent data indicate a similar proportion of patients using tramadol meet criteria for substance misuse or abuse as patients using more potent opioids (9).

It is a prodrug that is metabolized in the liver by the cytochrome P450 enzymes CYP2D6 and CYP3A4 to more potent opioid metabolites, most importantly the O-demethylation product M1. As with codeine, patients can be poor or rapid metabolizers of tramadol based on their CYP alleles (91). Thus, poor metabolizers of tramadol mediated by CYP2D6 have lower levels of the major M1 active metabolite, reducing its analgesic effects (92). Tapentadol is a μ-opioid agonist that also acts as a noradrenaline-reuptake inhibitor.

There is evidence that tramadol can partially relieve neuropathic pain (27) and it is considered second-line treatment for neuropathic pain (21-23). Tramadol has been found to have anxiolytic effects in rats that are mediated through opioid receptors (91). For neuropathic pain it has been found to have a NNT of 4.7 (95% CI 3.6-6.7) and a NNH of 12.6 (95% CI 8.4–25.3) (22). The efficacy of tapentadol in treating neuropathic pain is limited. One study that showed potential utility of tapentadol may have been confounded by the unmasking of patients in the trial, while it was not found to be efficacious in another trial. As such, the NeuPSIG of the IASP do not recommend its use for neuropathic pain (22). Tapentadol and extended-release forms of tramadol have been suggested as alternatives to other opioids in the treatment of other chronic pain conditions such as osteoarthritis and lower back pain (93).

Benzodiazepines

Benzodiazepines are not analgesics, but up to one third of patients taking chronic opioids for non-cancer pain have reported concurrent benzodiazepine use (9, 94, 95), and concurrent use of opioids and benzodiazepines is a consistent, strong predictor of problematic opioid use (9),

and increased risk of overdose (96, 97). Benzodiazepines act as allosteric modulators on the GABA-a receptor. This ligand-gated ion channel is inhibitory in nature, reducing neuron excitability, resulting in possible sedative, amnestic and anticonvulsant effects depending on the receptor subtypes (98). Benzodiazepines may be prescribed appropriately for anxiety disorders, which have been found to be more prevalent in patients with chronic pain than in the general population (99). They may be also occasionally prescribed for painful spastic conditions such as multiple sclerosis (100). Benzodiazepines, studied in four trials, have evidence for the short-term relief of non-specific low-back pain, but generally have less evidence than non-benzodiazepine muscle relaxants (101). Patients using benzodiazepines concurrently with opioids or other analgesic medications must be monitored closely for signs of toxicity, or misuse and abuse. Of note, even use of benzodiazepines alone are poorly tolerated, especially in those older than 65, and are associated with anticholinergic side effects, sedation and an elevated risk of falls (102).

Cannabis

A few small trials in patients suffering from PDN, HIV-associated neuropathy and post-traumatic/post-surgical neuropathic pain have shown cannabis to be more efficacious than placebo for analgesia (103-108). However, there have been no large randomized controlled trials examining the efficacy of medical cannabis in various pain syndromes. No dosing guidelines are available, and it is unclear which of the at least 489 distinct compounds from 18 different chemical classes contained in cannabis is responsible for any analgesic effects (109). Despite this, cannabinoids are now considered a third-line treatment for neuropathic pain in

the 2014 consensus statement on managing chronic neuropathic pain from the Canadian Pain Society (23). The 2010 European guidelines only recommend cannabinoids as 4th line treatment for central pain secondary to multiple sclerosis and refractory peripheral neuropathic pain (20).

Several reviews have attempted to summarize and draw conclusions on the tolerability and effectiveness of cannabis-based medications for chronic neuropathic pain. A Cochrane review found no high quality evidence for efficacy of any cannabis-based medicine for treatment of any condition with chronic neuropathic pain, and found concern regarding adverse events including somnolence, sedation, confusion and psychosis. Another recent review by Lynch et al found cannabinoids to be "modestly" effective, while Boychuk et al concluded cannabis-based medications could be an alternative for chronic neuropathic pain (110, 111). Based on these reviews the 2014 Canadian Pain Society Consensus Statement on Chronic Neuropathic Pain suggested using cannabinoids as a third-line agent for management of neuropathic pain (23).

The endogenous cannabinoid system consists of the ligands N-arachidonoylethanolamine (anandamide or AEA) and 2-arachidonoylglycerol (2-AG) that bind the G-protein coupled cannabinoid 1 and 2 receptors (CB1 and CB2) (112, 113). These receptors are also bound and activated by the phytocannabinoids delta-9 tetrahydrocannabinol (Δ9-THC), Δ8-THC, and cannabinol (CBN) from cannabis sitava, or marijuana. Activation of the CB1 or CB2 receptors by endo- or phytocannabinoids inhibits adenylyl cyclase activity, resulting in decreased formation of cyclic adenosine monophosphate (cAMP) (112). This decrease in cAMP leads to the

inhibition of neurotransmitter release in the CNS (112, 113), including 5-HT, glutamate, ACh, γ-Aminobutyric acid (GABA), and NE (113).

Δ9-THC is responsible for the psychoactive effects of cannabis (114) while cannabidiol (CBD) is thought to possess anti-inflammatory and analgesic properties. Cannabidiol does not appear to act through the CB1 receptors at physiological concentrations (115) and has minimal psychotropic effects.

There is concern regarding the use of cannabis and its mental health effects, particularly the risk of developing psychosis with its use, although studies have had conflicted results. The adverse effects of marijuana use in adolescence has been associated with impaired judgement leading to risky behaviour, altered brain development and cognitive impairment, acute paranoia and psychosis, and chronic psychotic disorders in patients with a predisposition to such disorders (116, 117). In adults the data is controversial. In a large longitudinal study, the National Epidemiologic Survey on Alcohol and Related Conditions, 34,653 adult respondents were interviewed twice, 3 years apart, about their mental health status and substance use. In a cross-sectional analysis of the data in 2015, cannabis use was found to be associated with the development of bipolar disorder, panic disorder with agoraphobia, and social phobia (118). In a separate longitudinal analysis of the data in 2016, however, marijuana use was not found to be associated with mood disorders in the 3 year follow up interview, although it was significantly associated with substance use disorder on follow up (119). These studies are limited by the fact that they are association studies only, and cannabis users were divided in broad groups in terms

of the amount used, which may not account for important differences in the pattern of use. It was not indicated whether patients were using marijuana for recreational or medical purposes, and these may be very distinct populations. Further prospective research is needed to assess the risks and benefits of medical marijuana use for pain, and until further scientific data is available medical cannabis should continue to be limited to adults.

Conclusions

The pharmacological management of pain overlaps substantially with that of psychological disorders reflecting common neuronal pathways. Modulation of the noradrenergic system appears to play a central role in both analgesia and mood stabilization. In patients with concurrent pain and mood disorders, the selection of a medication such as a SNRI, gabapentinoid or weak opioid with SNRI effects may improve both conditions, and the appropriate treatment of psychological comorbidities often confers a beneficial effect on chronic pain. There is weak evidence that benzodiazepines may be useful in treating back pain, and they have a well-established role in managing anxiety disorders, so they may be considered for short term therapy in patients with concurrent anxiety disorders and low back pain, recognizing their addictive potential, and increased risk of overdose in patients using opioids.

It is important to recognize that pain patients with concurrent psychological disorders are at increased risk of misusing opioids, and benzodiazepines increase the risk of both adverse events and substance misuse in patients using opioids. Therefore careful consideration should be given before prescribing opioids for chronic non-cancer pain in patients with a history of

depression, anxiety, PTSD or substance use disorder, and benzodiazepines generally should bot be prescribed concurrently with opioids, especially in these patients. Anxiety in these patients would be more safely managed with a SSRI or SNRI. Most patients would also benefit from non-pharmacological interventions for their concurrent mood and pain disorders, such as cognitive behavioural therapy, although this is often prohibited by cost.

As cannabis becomes legalized in several countries, it will become more widely prescribed for chronic pain as well as other conditions, the risk and benefit for cannabis use in each patient must be assessed and patients must be monitored closely for the development of psychological disorders. There is moderate evidence for the use of cannabinoids in treating neuropathic pain, and it is suggested as a third line agent by the Canadian Pain Society for management of chronic neuropathic pain. Even so, cannabinoids should be avoided in patients with a personal history or family history of psychosis, and in patients younger than 25 years of age. Patients who are deemed appropriate for therapy with cannabinoids should be advised to start with a low dose and to give adequate time for effect so as to avoid adverse psychotropic effects from consuming too much.

Given the substantial overlap in both the biology, pharmacotherapy and psychological treatment of pain and psychological disorders these patients are best managed in a multidisciplinary setting with collaboration between pain physicians, psychiatrists and psychologists.

Table 1. Dosing of antidepressant medications for depression and pain.

Medications	Antidepressant Dose	Pain Dose
Amitriptyline	100 – 300 mg daily	25 – 150 mg daily
Nortriptyline	75 – 150 mg daily	25 – 150 mg daily
Duloxetine	60 – 120 mg daily	60 mg daily
Venlafaxine	75 – 225 mg daily	37.5 – 225 mg daily
Desvenlafaxine	50 – 100 mg daily	200 - 400 mg daily

References

1. Azam MA, A.Z. W, Montbriand J, Burns LC, McMillan K, Clarke H, et al. Acceptance and Commitment Therapy to Manage Pain and Opioid Use after Major Surgery: Preliminary Outcomes from the Toronto General Hospital Transitional Pain Service. Can J Pain. 2017;In Press.
2. Fine L. Sleep: important considerations in management of pain. Physical medicine and rehabilitation clinics of North America. 2015;26(2):301-8.
3. Hooten WM. Chronic Pain and Mental Health Disorders: Shared Neural Mechanisms, Epidemiology, and Treatment. Mayo Clinic proceedings. 2016;91(7):955-70.
4. Becker WC, Sullivan LE, Tetrault JM, Desai RA, Fiellin DA. Non-medical use, abuse and dependence on prescription opioids among U.S. adults: psychiatric, medical and substance use correlates. Drug Alcohol Depend. 2008;94(1-3):38-47.
5. Liebschutz JM, Saitz R, Weiss RD, Averbuch T, Schwartz S, Meltzer EC, et al. Clinical factors associated with prescription drug use disorder in urban primary care patients with chronic pain. J Pain. 2010;11(11):1047-55.
6. Tetrault JM, Desai RA, Becker WC, Fiellin DA, Concato J, Sullivan LE. Gender and non-medical use of prescription opioids: results from a national US survey. Addiction. 2008;103(2):258-68.
7. Fischer B, Lusted A, Roerecke M, Taylor B, Rehm J. The prevalence of mental health and pain symptoms in general population samples reporting nonmedical use of prescription opioids: a systematic review and meta-analysis. J Pain. 2012;13(11):1029-44.
8. Wasan AD, Butler SF, Budman SH, Benoit C, Fernandez K, Jamison RN. Psychiatric history and psychologic adjustment as risk factors for aberrant drug-related behavior among patients with chronic pain. Clin J Pain. 2007;23(4):307-15.
9. Morley KI, Ferris J, Winstock AR, Lynskey MT. Polysubstance use and misuse or abuse of prescription opioid analgesics: A multi-level analysis of international data. Pain. 2017.
10. Weinrib AZ, Burns LC, Mu A, Azam MA, Ladak SS, McRae K, et al. A case report on the treatment of complex chronic pain and opioid dependence by a multidisciplinary transitional pain service using the ACT Matrix and buprenorphine/naloxone. J Pain Res. 2017;10:747-55.
11. Paoli F, Darcourt G, Cossa P. [Preliminary note on the action of imipramine in painful states]. Rev Neurol (Paris). 1960;102:503-4.
12. Gillman PK. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. Br J Pharmacol. 2007;151(6):737-48.
13. Cusack B, Nelson A, Richelson E. Binding of antidepressants to human brain receptors: focus on newer generation compounds. Psychopharmacology (Berl). 1994;114(4):559-65.
14. Sills MA, Loo PS. Tricyclic antidepressants and dextromethorphan bind with higher affinity to the phencyclidine receptor in the absence of magnesium and L-glutamate. Mol Pharmacol. 1989;36(1):160-5.
15. Richelson E. Antimuscarinic and other receptor-blocking properties of antidepressants. Mayo Clinic proceedings. 1983;58(1):40-6.
16. Eisenach JC, Gebhart GF. Intrathecal amitriptyline acts as an N-methyl-D-aspartate receptor antagonist in the presence of inflammatory hyperalgesia in rats. Anesthesiology. 1995;83(5):1046-54.

17. Derry S, Wiffen PJ, Aldington D, Moore RA. Nortriptyline for neuropathic pain in adults. Cochrane Database Syst Rev. 2015;1:CD011209.
18. Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. Cochrane Database Syst Rev. 2014(1):CD007115.
19. Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain in adults. Cochrane Database Syst Rev. 2015(7):CD008242.
20. Attal N, Cruccu G, Baron R, Haanpaa M, Hansson P, Jensen TS, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol. 2010;17(9):1113-e88.
21. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain. 2007;132(3):237-51.
22. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015;14(2):162-73.
23. Moulin D, Boulanger A, Clark AJ, Clarke H, Dao T, Finley GA, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. Pain Res Manag. 2014;19(6):328-35.
24. Meister R, von Wolff A, Mohr H, Harter M, Nestoriuc Y, Holzel L, et al. Comparative Safety of Pharmacologic Treatments for Persistent Depressive Disorder: A Systematic Review and Network Meta-Analysis. PloS one. 2016;11(5):e0153380.
25. Pacher P, Kecskemeti V. Cardiovascular Side Effects of New Antidepressants and Antipsychotics: New Drugs, old Concerns? Current pharmaceutical design. 2004;10(20):2463-75.
26. Sindrup SH, Otto M, Finnerup NB, Jensen TS. Antidepressants in the treatment of neuropathic pain. Basic Clin Pharmacol Toxicol. 2005;96(6):399-409.
27. Kremer M, Salvat E, Muller A, Yalcin I, Barrot M. Antidepressants and gabapentinoids in neuropathic pain: Mechanistic insights. Neuroscience. 2016;338:183-206.
28. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. Cochrane Database Syst Rev. 2007(4):CD005454.
29. Krell HV, Leuchter AF, Cook IA, Abrams M. Evaluation of reboxetine, a noradrenergic antidepressant, for the treatment of fibromyalgia and chronic low back pain. Psychosomatics. 2005;46(5):379-84.
30. Marchand F, Alloui A, Chapuy E, Jourdan D, Pelissier T, Ardid D, et al. Evidence for a monoamine mediated, opioid-independent, antihyperalgesic effect of venlafaxine, a non-tricyclic antidepressant, in a neurogenic pain model in rats. Pain. 2003;103(3):229-35.
31. Nakajima K, Obata H, Iriuchijima N, Saito S. An increase in spinal cord noradrenaline is a major contributor to the antihyperalgesic effect of antidepressants after peripheral nerve injury in the rat. Pain. 2012;153(5):990-7.
32. Bohren Y, Tessier LH, Megat S, Petitjean H, Hugel S, Daniel D, et al. Antidepressants suppress neuropathic pain by a peripheral beta2-adrenoceptor mediated anti-TNFalpha mechanism. Neurobiol Dis. 2013;60:39-50.

33. Sud R, Spengler RN, Nader ND, Ignatowski TA. Antinociception occurs with a reversal in alpha 2-adrenoceptor regulation of TNF production by peripheral monocytes/macrophages from pro- to anti-inflammatory. Eur J Pharmacol. 2008;588(2-3):217-31.
34. Zhu J, Wei X, Feng X, Song J, Hu Y, Xu J. Repeated administration of mirtazapine inhibits development of hyperalgesia/allodynia and activation of NF-kappaB in a rat model of neuropathic pain. Neurosci Lett. 2008;433(1):33-7.
35. McCleskey EW, Gold MS. Ion channels of nociception. Annu Rev Physiol. 1999;61:835-56.
36. Carr DB, Goudas LC. Acute pain. Lancet. 1999;353(9169):2051-8.
37. Besson JM. The neurobiology of pain. Lancet. 1999;353(9164):1610-5.
38. Levine JD, Fields HL, Basbaum AI. Peptides and the primary afferent nociceptor. J Neurosci. 1993;13(6):2273-86.
39. Sommer C. Painful neuropathies. Current opinion in neurology. 2003;16(5):623-8.
40. Marchand F, Perretti M, McMahon SB. Role of the immune system in chronic pain. Nature reviews Neuroscience. 2005;6(7):521-32.
41. Bohren Y, Karavelic D, Tessier LH, Yalcin I, Gaveriaux-Ruff C, Kieffer BL, et al. Mu-opioid receptors are not necessary for nortriptyline treatment of neuropathic allodynia. Eur J Pain. 2010;14(7):700-4.
42. Megat S, Bohren Y, Doridot S, Gaveriaux-Ruff C, Kieffer BL, Freund-Mercier MJ, et al. kappa-Opioid receptors are not necessary for the antidepressant treatment of neuropathic pain. Br J Pharmacol. 2015;172(4):1034-44.
43. Mico JA, Ardid D, Berrocoso E, Eschalier A. Antidepressants and pain. Trends Pharmacol Sci. 2006;27(7):348-54.
44. Perahia DG, Pritchett YL, Desaiah D, Raskin J. Efficacy of duloxetine in painful symptoms: an analgesic or antidepressant effect? Int Clin Psychopharmacol. 2006;21(6):311-7.
45. Hearn L, Derry S, Phillips T, Moore RA, Wiffen PJ. Imipramine for neuropathic pain in adults. Cochrane Database Syst Rev. 2014(5):CD010769.
46. Bandelow B, Zohar J, Hollander E, Kasper S, Moller HJ, Wfsbp Task Force on Treatment Guidelines for Anxiety O-C, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders - first revision. World J Biol Psychiatry. 2008;9(4):248-312.
47. Vranken JH, Hollmann MW, van der Vegt MH, Kruis MR, Heesen M, Vos K, et al. Duloxetine in patients with central neuropathic pain caused by spinal cord injury or stroke: a randomized, double-blind, placebo-controlled trial. Pain. 2011;152(2):267-73.
48. Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, et al. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA. 2013;309(13):1359-67.
49. Skljarevski V, Zhang S, Desaiah D, Alaka KJ, Palacios S, Miazgowski T, et al. Duloxetine versus placebo in patients with chronic low back pain: a 12-week, fixed-dose, randomized, double-blind trial. J Pain. 2010;11(12):1282-90.
50. Skljarevski V, Zhang S, Chappell AS, Walker DJ, Murray I, Backonja M. Maintenance of effect of duloxetine in patients with chronic low back pain: a 41-week uncontrolled, dose-blinded study. Pain Med. 2010;11(5):648-57.

51. Schukro RP, Oehmke MJ, Geroldinger A, Heinze G, Kress HG, Pramhas S. Efficacy of Duloxetine in Chronic Low Back Pain with a Neuropathic Component: A Randomized, Double-blind, Placebo-controlled Crossover Trial. Anesthesiology. 2016;124(1):150-8.
52. Wang ZY, Shi SY, Li SJ, Chen F, Chen H, Lin HZ, et al. Efficacy and Safety of Duloxetine on Osteoarthritis Knee Pain: A Meta-Analysis of Randomized Controlled Trials. Pain Med. 2015;16(7):1373-85.
53. Gallagher HC, Gallagher RM, Butler M, Buggy DJ, Henman MC. Venlafaxine for neuropathic pain in adults. Cochrane Database Syst Rev. 2015(8):CD011091.
54. Allen R, Sharma U, Barlas S. Clinical experience with desvenlafaxine in treatment of pain associated with diabetic peripheral neuropathy. J Pain Res. 2014;7:339-51.
55. Allen R, Sharma U, Barlas S. Clinical Experience With Desvenlafaxine in Treatment of Patients With Fibromyalgia Syndrome. Clin Pharmacol Drug Dev. 2016.
56. Coplan JD, Aaronson CJ, Panthangi V, Kim Y. Treating comorbid anxiety and depression: Psychosocial and pharmacological approaches. World J Psychiatry. 2015;5(4):366-78.
57. Blanco C, Bragdon LB, Schneier FR, Liebowitz MR. The evidence-based pharmacotherapy of social anxiety disorder. Int J Neuropsychopharmacol. 2013;16(1):235-49.
58. Berlin RK, Butler PM, Perloff MD. Gabapentin Therapy in Psychiatric Disorders: A Systematic Review. Prim Care Companion CNS Disord. 2015;17(5).
59. Darba J, Kaskens L, Perez C, Alvarez E, Navarro-Artieda R, Sicras-Mainar A. Pharmacoeconomic outcomes for pregabalin: a systematic review in neuropathic pain, generalized anxiety disorder, and epilepsy from a Spanish perspective. Adv Ther. 2014;31(1):1-29.
60. Leung JG, Hall-Flavin D, Nelson S, Schmidt KA, Schak KM. The role of gabapentin in the management of alcohol withdrawal and dependence. Ann Pharmacother. 2015;49(8):897-906.
61. Eroglu C, Allen NJ, Susman MW, O'Rourke NA, Park CY, Ozkan E, et al. Gabapentin receptor alpha2delta-1 is a neuronal thrombospondin receptor responsible for excitatory CNS synaptogenesis. Cell. 2009;139(2):380-92.
62. Li Z, Taylor CP, Weber M, Piechan J, Prior F, Bian F, et al. Pregabalin is a potent and selective ligand for alpha(2)delta-1 and alpha(2)delta-2 calcium channel subunits. Eur J Pharmacol. 2011;667(1-3):80-90.
63. Field MJ, Li Z, Schwarz JB. Ca2+ channel alpha2-delta ligands for the treatment of neuropathic pain. J Med Chem. 2007;50(11):2569-75.
64. Matsuzawa R, Fujiwara T, Nemoto K, Fukushima T, Yamaguchi S, Akagawa K, et al. Presynaptic inhibitory actions of pregabalin on excitatory transmission in superficial dorsal horn of mouse spinal cord: further characterization of presynaptic mechanisms. Neurosci Lett. 2014;558:186-91.
65. Luo ZD, Calcutt NA, Higuera ES, Valder CR, Song YH, Svensson CI, et al. Injury type-specific calcium channel alpha 2 delta-1 subunit up-regulation in rat neuropathic pain models correlates with antiallodynic effects of gabapentin. J Pharmacol Exp Ther. 2002;303(3):1199-205.
66. Luo ZD, Chaplan SR, Higuera ES, Sorkin LS, Stauderman KA, Williams ME, et al. Upregulation of dorsal root ganglion (alpha)2(delta) calcium channel subunit and its correlation with allodynia in spinal nerve-injured rats. J Neurosci. 2001;21(6):1868-75.

67. Lee BS, Jun IG, Kim SH, Park JY. Intrathecal gabapentin increases interleukin-10 expression and inhibits pro-inflammatory cytokine in a rat model of neuropathic pain. Journal of Korean medical science. 2013;28(2):308-14.
68. Cheng J-K, Chiou L-C. Mechanisms of the Antinociceptive Action of Gabapentin. Journal of Pharmacological Sciences. 2006;100(5):471-86.
69. Patel R, Dickenson AH. Mechanisms of the gabapentinoids and alpha 2 delta-1 calcium channel subunit in neuropathic pain. Pharmacology research & perspectives. 2016;4(2):e00205.
70. Bauer CS, Nieto-Rostro M, Rahman W, Tran-Van-Minh A, Ferron L, Douglas L, et al. The increased trafficking of the calcium channel subunit alpha2delta-1 to presynaptic terminals in neuropathic pain is inhibited by the alpha2delta ligand pregabalin. J Neurosci. 2009;29(13):4076-88.
71. Xiao W, Boroujerdi A, Bennett GJ, Luo ZD. Chemotherapy-evoked painful peripheral neuropathy: analgesic effects of gabapentin and effects on expression of the alpha-2-delta type-1 calcium channel subunit. Neuroscience. 2007;144(2):714-20.
72. Coderre TJ, Kumar N, Lefebvre CD, Yu JS. Evidence that gabapentin reduces neuropathic pain by inhibiting the spinal release of glutamate. J Neurochem. 2005;94(4):1131-9.
73. Moore RA, Wiffen PJ, Derry S, Toelle T, Rice AS. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2014(4):CD007938.
74. Wiffen PJ, Derry S, Bell RF, Rice AS, Tolle TR, Phillips T, et al. Gabapentin for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2017;6:CD007938.
75. Arnold LM, Goldenberg DL, Stanford SB, Lalonde JK, Sandhu HS, Keck PE, Jr., et al. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. Arthritis Rheum. 2007;56(4):1336-44.
76. Moore RA, Straube S, Wiffen PJ, Derry S, McQuay HJ. Pregabalin for acute and chronic pain in adults. Cochrane Database Syst Rev. 2009(3):CD007076.
77. Antal M, Petko M, Polgar E, Heizmann CW, Storm-Mathisen J. Direct evidence of an extensive GABAergic innervation of the spinal dorsal horn by fibres descending from the rostral ventromedial medulla. Neuroscience. 1996;73(2):509-18.
78. Basbaum AI, Clanton CH, Fields HL. Three bulbospinal pathways from the rostral medulla of the cat: an autoradiographic study of pain modulating systems. J Comp Neurol. 1978;178(2):209-24.
79. Duggan AW, Griersmith BT. Inhibition of the spinal transmission of nociceptive information by supraspinal stimulation in the cat. Pain. 1979;6(2):149-61.
80. Pleuvry BJ. Opioid receptors and their relevance to anaesthesia. Br J Anaesth. 1993;71(1):119-26.
81. Shafer SL, Varvel JR. Pharmacokinetics, pharmacodynamics, and rational opioid selection. Anesthesiology. 1991;74(1):53-63.
82. Stein C. The control of pain in peripheral tissue by opioids. N Engl J Med. 1995;332(25):1685-90.
83. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. Pain Physician. 2008;11(2 Suppl):S133-53.
84. Charbogne P, Kieffer BL, Befort K. 15 years of genetic approaches in vivo for addiction research: Opioid receptor and peptide gene knockout in mouse models of drug abuse. Neuropharmacology. 2014;76 Pt B:204-17.

85. McDonald J, Lambert DG. Opioid receptors. Continuing Education in Anaesthesia Critical Care & Pain. 2005;5(1):22-5.
86. Buntin-Mushock C, Phillip L, Moriyama K, Palmer PP. Age-Dependent Opioid Escalation in Chronic Pain Patients. Anesthesia & Analgesia. 2005;100(6):1740-5.
87. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain. 2015;156(4):569-76.
88. Noble M, Treadwell JR, Tregear SJ, Coates VH, Wiffen PJ, Akafomo C, et al. Long-term opioid management for chronic noncancer pain. Cochrane Database Syst Rev. 2010(1):CD006605.
89. Kaye AD, Jones MR, Kaye AM, Ripoll JG, Galan V, Beakley BD, et al. Prescription Opioid Abuse in Chronic Pain: An Updated Review of Opioid Abuse Predictors and Strategies to Curb Opioid Abuse: Part 1. Pain Physician. 2017;20(2S):S93-S109.
90. Kaye AD, Jones MR, Kaye AM, Ripoll JG, Jones DE, Galan V, et al. Prescription Opioid Abuse in Chronic Pain: An Updated Review of Opioid Abuse Predictors and Strategies to Curb Opioid Abuse (Part 2). Pain Physician. 2017;20(2S):S111-S33.
91. de Souza Fiaes GC, Roncon CM, Sestile CC, Maraschin JC, Souza RL, Porcu M, et al. Panicolytic-like effect of tramadol is mediated by opioid receptors in the dorsal periaqueductal grey. Behav Brain Res. 2017;326:52-8.
92. Gong L, Stamer UM, Tzvetkov MV, Altman RB, Klein TE. PharmGKB summary: tramadol pathway. Pharmacogenet Genomics. 2014;24(7):374-80.
93. Afilalo M, Etropolski MS, Kuperwasser B, Kelly K, Okamoto A, Van Hove I, et al. Efficacy and safety of Tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. Clinical drug investigation. 2010;30(8):489-505.
94. Nielsen S, Lintzeris N, Bruno R, Campbell G, Larance B, Hall W, et al. Benzodiazepine use among chronic pain patients prescribed opioids: associations with pain, physical and mental health, and health service utilization. Pain Med. 2015;16(2):356-66.
95. Park TW, Saitz R, Ganoczy D, Ilgen MA, Bohnert AS. Benzodiazepine prescribing patterns and deaths from drug overdose among US veterans receiving opioid analgesics: case-cohort study. BMJ. 2015;350:h2698.
96. Jann M, Kennedy WK, Lopez G. Benzodiazepines: a major component in unintentional prescription drug overdoses with opioid analgesics. J Pharm Pract. 2014;27(1):5-16.
97. Jones JD, Mogali S, Comer SD. Polydrug abuse: a review of opioid and benzodiazepine combination use. Drug Alcohol Depend. 2012;125(1-2):8-18.
98. Griffin CE. Benzodiazepine Pharmacology and Central Nervous System–Mediated Effects. 2013;13(2):214-23.
99. McWilliams LA, Cox BJ, Enns MW. Mood and anxiety disorders associated with chronic pain: an examination in a nationally representative sample. Pain. 2003;106(1-2):127-33.
100. Lapeyre E, Kuks JB, Meijler WJ. Spasticity: revisiting the role and the individual value of several pharmacological treatments. NeuroRehabilitation. 2010;27(2):193-200.
101. van Tulder MW, Touray T, Furlan AD, Solway S, Bouter LM. Muscle relaxants for non-specific low back pain. Cochrane Database Syst Rev. 2003(2):CD004252.

102. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. Journal of the American Geriatrics Society. 2012;60(4):616-31.
103. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology. 2007;68(7):515-21.
104. Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology. 2009;34(3):672-80.
105. Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy. J Pain. 2015;16(7):616-27.
106. Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ. 2010;182(14):E694-701.
107. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain. 2013;14(2):136-48.
108. Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain. 2008;9(6):506-21.
109. Elsohly MA, Slade D. Chemical constituents of marijuana: the complex mixture of natural cannabinoids. Life Sci. 2005;78(5):539-48.
110. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. Journal of pain and symptom management. 2014;47(1):166-73.
111. Boychuk DG, Goddard G, Mauro G, Orellana MF. The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. Journal of oral & facial pain and headache. 2015;29(1):7-14.
112. De Petrocellis L, Di Marzo V. An introduction to the endocannabinoid system: from the early to the latest concepts. Best practice & research Clinical endocrinology & metabolism. 2009;23(1):1-15.
113. Serrano A, Parsons LH. Endocannabinoid influence in drug reinforcement, dependence and addiction-related behaviors. Pharmacology & therapeutics. 2011;132(3):215-41.
114. Hajos N, Ledent C, Freund TF. Novel cannabinoid-sensitive receptor mediates inhibition of glutamatergic synaptic transmission in the hippocampus. Neuroscience. 2001;106(1):1-4.
115. Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. Trends Pharmacol Sci. 2009;30(10):515-27.
116. Fergusson DM, Boden JM. Cannabis use and later life outcomes. Addiction. 2008;103(6):969-76; discussion 77-8.
117. Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. N Engl J Med. 2014;370(23):2219-27.
118. Cougle JR, Hakes JK, Macatee RJ, Chavarria J, Zvolensky MJ. Quality of life and risk of psychiatric disorders among regular users of alcohol, nicotine, and cannabis: An analysis of the National Epidemiological Survey on Alcohol and Related Conditions (NESARC). Journal of psychiatric research. 2015;66-67:135-41.

119. Blanco C, Hasin DS, Wall MM, Florez-Salamanca L, Hoertel N, Wang S, et al. Cannabis Use and Risk of Psychiatric Disorders: Prospective Evidence From a US National Longitudinal Study. JAMA psychiatry. 2016;73(4):388-95.

Highlights

- There is significant overlap in the pharmacological management of both pain and psychological disorders
- Drugs originally developed as antidepressants and anticonvulsants are make up the first line treatments for chronic neuropathic pain
- Treatment of pain and psychological disorders warrants a multidisciplinary approach