NUNO DUARTE · JOSÉ PEDRAZA · MARLENE SANTOS

analgesic treatment in non-cancer chronic pain

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Escola Superior de Saúde do Instituto Politécnico do Porto

Porto, Portugal

Autores

Nuno Duarte

José Pedraza

Marlene Santos

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Overview

This book has been developed to support the curricular units of the Bachelor and Master study cycles of the School of Health of the Polytechnic Institute of Porto, which address the analgesic pharmacotherapy of chronic non-cancer pain.

The aim of this book is to provide an overview of the pharmacological agents used in the treatment of chronic pain, focusing on the mechanism of action, indications, and adverse effects. This book analyzed the information available in articles on conventional drugs used in the treatment of chronic pain, including randomized controlled trials, open trials, and systematic reviews with or without meta-analysis. Newer drugs with potential off-label use were also included. Information on outcomes related to pain relief, safety/tolerability profile, or both was also included.

1. Introduction

In 1986 the analgesic ladder is first mentioned in a publication from the World Health Organization (WHO) regarding cancer pain and has since been a core reference when treating pain. Briefly, the concept states that relieving pain in cancer patients ought to be started as quickly as possible, in a sequential manner with a non-opioid drug and proceed to a weak opioid if pain isn't successfully controlled, ending on a strong opioid if weak opioids are ineffective. On all these steps, adjuvant drugs can be added to improve pain management (1). Although a relatively simple concept, the analgesic ladder, introduced for cancer pain, helped terminally ill patients providing them more comfort and *"...legitimized the use of opioids, overcoming prejudicial and regulatory stigmas that had hampered compassionate pain care..."*(2). Since then, the principles of the analgesic ladder were applied in other pain contexts with different results. Indeed, the titration of analgesic classes and doses are helpful in acute or end of life pain. Conversely, when used in chronic non cancer pain and in patients that use opioids, high rates of addiction, loss of efficacy, cognitive impairment, poor quality of life among other adverse consequences were observed, proving that in complex chronic pain conditions, the analgesic ladder is not appropriate (2).

Pain signaling involves transmission via afferent neurons, to the dorsal horn of the spinal cord, were interneurons, and ascending fibers modulate and transmit the signal to the brainstem and upper brain structures such as the thalamus, anterior cingulate cortex, or the prefrontal cortices, responsible for not only the sensory component but also the affective component of pain (3). Chronic pain is not a mere temporal continuum of acute pain. Various phenotypic modifications occur, resulting from structural plasticity in synapses and cell changes in pain pathways which will, overtime result in the "chronification" of pain (4). Moreover, neurochemistry changes on these pathways also concur to central sensitization, like the release of excitatory neuropeptides such as glutamate which leads to up-regulation of NMDA receptors, or the downregulation of GABA receptors (5). The underlying changes mentioned are common to different chronic pain conditions, with distinct etiologies, although two main mechanisms can be considered, the neuropathic and the inflammatory component. Both can be present, or one may be prevalent over the other. Depending on which one is dominant, a multitude of pharmacological agents is available.

Pain resulting from inflammatory contexts can be tackled with non-steroidal anti-inflammatory (NSAID's) agents. When a neuropathic component manifests, antidepressants and anticonvulsants are considered, although if not satisfactory pain relief is achieved, opioids are an option. Cannabinoids are a promising lane for many types of pain, especially in fibromyalgia and when the former mentioned drugs fail. Considering this, the management and approach to chronic

pain in its different settings can vary, depending on the type of condition, etiology, comorbidities, and other variables.

The aim of this book is to provide an overview on the pharmacological agents used for chronic pain, emphasizing mechanism of action, indications, and adverse events. This book reviewed information available on papers for conventional drugs used in chronic pain management and included randomized controlled trials, open-label trials, and systematic reviews with or without meta-analysis. Recent drugs with potential "off-label" use were also included. Information regarding outcomes related to pain relief, safety profile/tolerability or both was also addressed.

2. Non-Steroidal Anti-Inflammatory Drugs

An heterogenous class of drugs widely used in pain conditions, the NSAID's are structurally very different from one another. All of them are acidic in nature which allows interaction with phospholipids, precursors of arachidonic acid, the substrate for cyclo-oxygenase (COX) and lipoxygenase enzymes. Prostaglandins, as well as leukotrienes, are pro-inflammatory eicosanoids synthetized on these enzymatic pathways and are capable of afferent nociceptor sensitization, activation, and chemotaxis responsible for pain with concomitant inflammation (6,7). NSAID's inhibit COX enzymes by acetylation (aspirin), and substrate analog binding (ibuprofen) (figure 1). Other mechanisms of action have been proposed for NSAID's besides its peripheral action. There is evidence of a putative central mechanism of action where supraspinal and spinal administration of NSAID's in nociception animal models produced antinociception (8). This mechanism is possibly related to inhibition of prostaglandin formation in the CNS, opioid modulation, activation of descending serotonin pathways and antagonization of NMDA receptor mediated hyperalgesia (7).

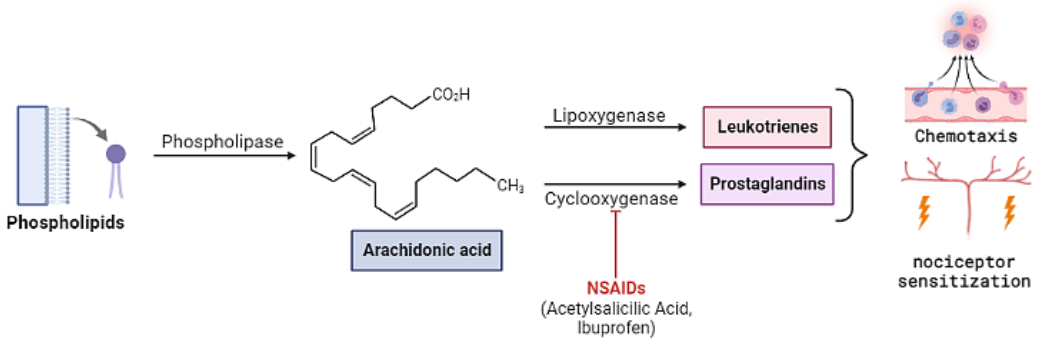

Figure 1 – Pathways involved in inflammation and the mechanism of action of nonsteroidal anti-inflammatory drugs (NSAIDs) in blocking COX pathway.

Despite the various mechanisms described, all NSAID's interact with the COX enzymes blocking their action which is also the basis for their adverse events profile. A 2012 meta-analysis reported that all NSAID's increased the risk of upper GI events, although risk ratio was lower for some molecules (ibuprofen, celecoxib, aceclofenac) compared to others (ketorolac and azapropazone) (9). Major vascular events such as non-fatal stroke and coronary events like myocardial infarction where some of the main outcomes of a 2013 meta-analysis conducted to evaluate the cardiovascular risk of NSAID's. The results showed an increased risk for diclofenac, ibuprofen, and naproxen (like coxibs), albeit in the latter a more favorable cardiovascular profile (10).

Both studies also found risks to be dose dependent. Regarding renal effects it is known that prostaglandin synthesis inhibition diminishes renal perfusion. Prostaglandins namely prostacyclins PGE2 and PGD2 produce vasodilation in the afferent arteriole of the Malpighi glomerulus ensuring adequate flow to the kidneys (11). Moreover, there is evidence that hypertension, heart failure, lupus nephritis and other diseases where renin-angiotensin-aldosterone axis and sympathetic triggers are more activated, have higher risk. This was demonstrated in a nested control-case study conducted in the UK where the risk of acute renal failure was 3-fold greater than in the general population. Patients with hypertension and heart failure were at even higher risk as well as patients taking diuretics and calcium channel blockers. Risk was present with long-term and short-term treatment and once again, risk increases in a dose dependent fashion (12).

While COX1 is constitutively expressed in most cells, COX-2 is inducible, only expressed in injuries and in some tissues and cells namely, macrophages, synovial fibroblasts, endothelial cells, osteoblasts, and chondrocytes (7,8). Hence, it was believed that developing new molecules with COX-2 selectivity would preserve the analgesic and anti-inflammatory effects without inducing adverse reactions, typical of non-selective NSAID's (13,14). This assumption was tested with the first large trials assessing efficacy and GI risk with rofecoxib and celecoxib. Coxibs presented less GI complications, since COX-1 is the main cytoprotective prostaglandin of the gastric mucosa, although it was recognized that COX-2 may be upregulated in patients with *Helicobacter pylori* infection (13,15). These results suggested that GI safety of coxibs may depend on preexisting risk conditions such as peptic ulcer and gastrointestinal bleeding history. The MEDAL trial was the first study comparing a coxib with a non-selective NSAID regarding thrombotic cardiovascular events in a long-term period. Etoricoxib showed no inferiority when compared to diclofenac on the composite endpoint for cardiovascular risk which included events like myocardial infarction, cerebrovascular thrombosis, pulmonary embolism, or angina pectoris to name a few (16). Some studies addressed the cardiovascular risk as well as the gastrointestinal (GI) risk using celecoxib as the intervention. Celecoxib exhibits less risk of recurrent GI bleeding in a chronic administration when compared to naproxen in a population of patients with arthritis and cardiovascular and thrombotic diseases (17). Moreover, in a trial of non-inferiority, celecoxib demonstrated similar cardiovascular risk to ibuprofen and naproxen and once again lower serious GI events (18). These results are even more important when considering that naproxen was used in both studies as the comparator, and it is perceived as the non-selective NSAID with the lowest cardiovascular risk (10).

NSAID's are the first pharmacological line of treatment recommended for osteoarthritis of the hand, hip, and knee (19). They are also recommended by most guidelines for acute and chronic low back pain and a better option for relieving pain when compared to paracetamol, the most used

drug for analgesia (20,21). In contrast, NSAID's seem to be non-effective in neuropathic pain and guidelines do not mention them, even though they are still prescribed as adjuvants in many neuropathic conditions (22,23). Their use extends to headaches, migraines, trauma, musculoskeletal injuries, and any other pain context presenting with an inflammatory component. Noteworthy is the fact that many of these drugs are over the counter (OTC) preparations available in many countries. Their undisputed efficacy in relieving pain makes them one of the most used drug classes even though they exhibit the safety profile described above. This is even more important if considered that most common users of NSAID's are elderly, especially in chronic use (24). In the USA, 50% of patients aged 65 years or more use 5 or more drugs for their diseases. This fact illustrates the potential for drug interaction and toxicity, since many of the patients are unaware of the risks, may use NSAID's at higher doses than recommended, for long periods of time and without a healthcare professional supervision (14).

Recommendations were published to manage and mitigate the frequency and severity of adverse events. The treatment should always be individualized, considering the patient risk factors. Moreover, long-term treatment is to be avoided with the lowest effective dose administered (19,25). Patients with GI risk factors should be treated with selective COX-2 NSAID's or add a gastroprotective agent such as a proton pump inhibitor (PPI). Importantly, although PPI's have a good safety profile and protect the upper GI tract, no protective effect has been found for lower GI tract. In addition, PPI's are not without risks, especially in chronic use, since it increases the risk of *Clostridium difficile* infection, hospitalization acquired pneumonia, altered absorption of vitamins and minerals, increased cardiovascular risk and a potential for drug interactions (6). Regarding cardiovascular risk, recommendations from the American Heart Association and the American College of Rheumatology agree that patients suffering from hypertension, ischemia, bypass surgery, history of myocardial infarction, edema, or other cardiovascular events should avoid NSAID's, particularly COX-2 selective agents. These drugs should only be used if other options are not effective (19,26) . In contrast, new data suggests that not all COX-2 inhibitors have a greater cardiovascular risk then non-selective NSAID's as already mentioned and may even be beneficial in the long-term. In a recent retrospective cohort with a 10 year follow up, it was found that etoricoxib and celecoxib may in fact be linked to a lower risk of ischemic stroke, giving credit to this assumption (27). Another strategy is the use of topical preparations of NSAID's which were found to be similarly effective to their oral counterparts for some joint and soft tissue disorders and injuries like osteoarthritis and knee pain (19,25,28).

In summary, NSAID's are a useful and proven drug class for many pain conditions, especially if an inflammatory component is present. Safety profile issues are important limitations when considering chronic use. New evidence regarding cardiovascular risk may change this in the future although for now patients with a history of cardiovascular events should avoid using these agents, unless if necessary and always assessing the risk/benefit ratio, in short-term or intermittent use.

3. Antidepressants

Depression and pain share many of the same neural pathways and it is suggested the two conditions co-exacerbate one another. Indeed, pain induces physical and psychological distress and patients presenting with major depressive disorder (MDD), often experience severe and chronic pain (figure 2). This knowledge formed the foundation which led to the use of antidepressants in chronic pain disorders for many decades now (29). The accumulated evidence demonstrates that tricyclic antidepressants (TCA's) and selective serotonin and norepinephrine reuptake inhibitors (SSNRI's) are effective in relieving pain, namely neuropathic conditions (22). In Table 1 a synopsis of the main antidepressants used in chronic pain conditions is presented.

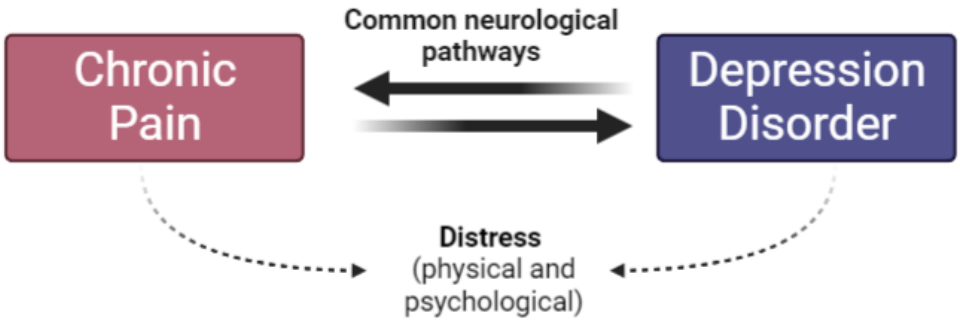

Figure 2 - Co-exacerbation between Chronic Pain and Depression.

3.1 Tricyclic Antidepressants

TCA's act by inhibiting the reuptake of 5-HT and norepinephrine thus potentiating inhibitory pain pathways (30,31). TCA's have similar molecular structure to MK-801 (NMDA antagonist), thus these agents are capable of binding to the NMDA receptor and block its action. NMDA receptors are implicated in central sensitization and mediate hyperalgesia (32). In addition, TCA's are known to interact with endogenous opioid production/action, since naloxone blocks the antinociceptive action of these agents (31,33). Moreover, TCA's exhibit voltage-gated sodium and calcium channel inhibition, which contribute to neuronal and nociceptive signaling (34,35). Other affects may contribute to analgesia. In a rat model of neuropathic pain, caffeine, a non-selective adenosine receptor antagonist blocked the antinociceptive effect of amitriptyline which suggest that TCA's may interact with the adenosine receptor (36). Finally, TCA's are known to exhibit anticholinergic and anti-histaminic effects which are also involved in nociceptive signaling.

Agents of this drug class have been used in a variety of conditions when a neuropathic component of pain may be involved. In patients with LBP, nortriptyline, the active metabolite of amitriptyline, showed a modest but significant decrease in pain intensity, particularly in the subgroup of patients with diagnosed radicular pain. No improvements were detected in other outcomes (disability, mood, QOL and physician rated outcome) (37). A double blinded randomized trial tested the efficacy of a low dose amitriptyline in non-specific LBP patients against an active comparator. Amitriptyline did not relieve pain at two measured time periods, although a significant improvement in disability was detected at 3 months with minimal adverse events (38). DNP is another indication for TCA's. Amitriptyline has been tested as monotherapy and in combination with other drugs demonstrating significant and similar results in pain relief and even a synergistic effect with pregabalin and duloxetine (39,40). Other pain conditions have been studied where TCA's showed significant results such as in PHN, phantom limb pain and nerve trauma (41). Evidence on fibromyalgia is also recognized. Amitriptyline and dosulepin improve all outcomes for this condition including sleep disorders and fatigue, but less on pain intensity giving weight to the theory that the analgesic effect is moderate (42). Regarding pain of rheumatic conditions (e.g., osteoarthritis) only duloxetine a SSNRI demonstrates efficacy although very modest and supported by few studies. TCA's and other drugs (anticonvulsants, SSRIs, other SSNRI's) do not have adequate evidence to support their use at present (19,25,43). In migraine prevention amitriptyline is the best studied TCA, exhibiting a considerable effect. Amitriptyline was found to reduce the likelihood of provoked cortical spreading depression in rats, a feature of classical migraines (42,44).

The advantage of being pleiotropic in nature, allows TCA's, to interact with many nociceptive pathways. Conversely, this drug class has a myriad of side effects for the same reason. Side effects as well as pain relief is dose dependent. Higher doses of amitriptyline (up to 75mg) resulted in additional pain relief with good tolerability, albeit with greater frequency of adverse effects (45). The most common side effects relate to the anticholinergic effects, like drowsiness, sedation, dry mouth, constipation, and weight gain. Hypotension and prolonged QT interval are not frequent as systematic review and meta-analysis stated. The authors believe these serious side effects have low frequency since analgesic doses are lower than doses to treat depression. Of note, nortriptyline and desipramine appear to produce more drowsiness than amitriptyline, while risk of headache is more likely with amitriptyline (46).

In summary, TCA's analgesia is of relevance in DNP, PHN, and LBP. Widespread pain like the one that occurs in fibromyalgia also responds to these agents. The main disadvantage of TCA's is their side effects profile albeit doses used for analgesia are usually well tolerated and withdrawal from treatment is low. Coupled with their low cost, TCA's, are first line agents and have been the

"gold standard" for neuropathic pain conditions. Care should be taken when a trial of TCA's is performed in the elderly, since side effects are more likely to occur. This is due to less capability to metabolize the drugs, more potential for interactions as well as increased likelihood of concomitant use of other molecules with anticholinergic effects. Despite all of this, it is noteworthy to mention that a Cochrane systematic review and meta-analysis stated that amitriptyline lacks strong evidence for its effectiveness in neuropathic pain. Indeed, the authors point out that all studies have methodology that does not meet current standards regarding design, reporting and conduct, thus are prone to numerous bias which probably overestimated the effects of amitriptyline. Nonetheless, they also acknowledge the benefits for tens of thousands of patients in decades of clinical use as well as the lack of reliable evidence of lack of effect, stating the potential benefit for some but not all patients (47).

3.2 Selective Serotonin and Norepinephrine Reuptake Inhibitors

The first studies conducted with venlafaxine to treat chronic pain started in the early 90's. One open label experience in 1996 reported treatment of 12 patients with neuropathic pain and headache. The authors found that venlafaxine could relieve pain in some of the patients with moderate efficacy, accompanied by some side effects such as nausea and hypertension, although this was a first trial with many limitations and bias (48). Nonetheless, a growing body of evidence supports its use especially when TCA's are not recommended because of their tolerability and anticholinergic activity. Venlafaxine acts by inhibiting reuptake of serotonin and norepinephrine without exhibiting NMDA and sodium channel antagonism or affinity for histaminergic and cholinergic receptors. Studies show that venlafaxine increases thresholds for pain summation and pain tolerance (49). Additionally, inhibition of α-2 adrenoreceptor is suggested to be involved in the analgesic effect of SSNRI's (50). Venlafaxine has similar effect to SSRIs in low doses since it has weak affinity to serotonin and adrenergic receptors, providing no meaningful analgesic effect. Conversely in higher doses, venlafaxine, and its active metabolite R-O-desmethylvenlafaxine show dual reuptake action and analgesic effect (49,50). This highlights the importance of the active metabolite and the higher and/or multiple dose regimen for analgesic effect of venlafaxine which usually is used in doses between 75mg up to 225mg (49–51). Venlafaxine in migraine prevention has been established in retrospective and prospective studies. Follow-up ranged from 2 to 6 months and included between 50 to 60 patients with migraines in doses from 75mg to 300mg with the primary outcome being the frequency of headaches. Results showed venlafaxine significantly decreased migraine frequency (52,53). Interestingly, a Cochrane review concluded that no strong evidence is provided for the use of SNRI's or SSRI's in migraine prevention, although the authors warn that this conclusion is based on follow-up of three months and more extensive trial periods are

needed (54). Regarding neuropathic pain conditions, the drug as demonstrated efficacy. Sindrup et al. compared venlafaxine (225mg/daily) to imipramine (150mg daily) and both to a placebo in a crossover trial of 12 weeks (4 weeks in each period) and concluded that summed pain scores have no difference between the two drugs, but both are lower than placebo. Numbers needed to treat (NNT) was also calculated as pain relief of at least 50% and found a significantly lower NNT for imipramine (2.7) when compared to venlafaxine (5.2) which indicates a superior effect in favor of TCA's (55). Worthy of mention is a later trial comparing venlafaxine to placebo in two daily doses, 75mg and 150mg-225mg in patients with DNP for 6 weeks. The results showed a significant decrease in pain intensity and a significant increase in pain relief measurements, the two primary outcomes. Secondary outcomes were also favorable to venlafaxine and NNT was 4.5 for the 150mg-225mg arm, thus lower than in the previous trial. Of note, the results were reported using the intention to treat (ITT) approach which considers dropouts. This is important since in Sindrup et al. the NNT of 2.6 for imipramine may be overestimated because data lost to follow-up was not considered (56). Another study evaluated for 8 weeks the ongoing neuropathic pain in 60 patients and the response to sensory tests like pin-prick hyperalgesia, allodynia, and pain thresholds to heat, and electrical stimuli. Likewise, venlafaxine was used in doses of 75mg/daily and 150mg/daily against placebo. Venlafaxine decreased pin-prick hyperalgesia and touch allodynia, two key features of neuropathic pain (57). These trials point to better results in DNP. Adverse events reported were mainly nausea and tiredness with low withdrawal rates and good tolerability. Oddly enough, a study developed to analyze the analgesic effect of venlafaxine in patients with neuropathic pain and spinal cord injury with concomitant MDD, found no benefit, except for patients exhibiting mixed pain (only when receiving 150mg/daily) and nociceptive pain. The authors explain this seemingly contradiction, by stating that neuropathic pain arising from spinal cord injury has a more central component with cortical rearrangements (58). One aspect that is common to all these studies is the concept that venlafaxine higher doses are important to the analgesic effect.

Duloxetine has similar action to venlafaxine and has been widely studied in neuropathic conditions and fibromyalgia. In DNP, duloxetine has shown moderate efficacy with good tolerability and low frequency of side effects compared to placebo as well as to amitriptyline and gabapentin (59–61). In recent years, interest in combining duloxetine with anticonvulsants for management of DNP to obtain a synergic effect was explored. The multinational COMBO-DN study reported a similar effect when combining pregabalin (300mg/daily) and duloxetine (60mg/daily) vs higher dose regimens in non-responders (600mg/daily-pregabalin and 120mg/daily -duloxetine) (62). Combination therapy may deliver higher pain relief (consistently reported albeit not statistically significant), and less probability of side effects and withdrawals. Regarding fibromyalgia, the BPI average pain severity score was evaluated on a few trials in the last decade and consistently

showed no significant decreases despite secondary outcomes like QOL, safety and function significantly improved (63–65). Interestingly, an improved function and improved pain intensity scores were seen with venlafaxine although the study was not placebo controlled, with very few reporting of study design and used methods (66). Since venlafaxine has fewer studies, it is used off label for fibromyalgia patients in contrast to duloxetine which is FDA approved for this condition. It is also recommended by the Canadian Pain Society guidelines and NICE guidelines for all neuropathic pain conditions except for trigeminal neuralgia (TN). Duloxetine and venlafaxine also have interest in osteoarthritis but once again studies with duloxetine are with larger, well-defined samples of patients with more robust designs (double-blinded, placebo controlled) (67,68). Recommendations for the use of duloxetine by the American College of Rheumatology/Arthritis in the treatment of osteoarthritis suggest a moderate effect. Duloxetine efficacy was also explored in chronic LBP. In a large randomized multinational placebo-controlled trial, duloxetine was used in 60 to 120mg/daily doses and was reported to be superior to placebo in primary outcome of BPI 24h average pain score as well as secondary outcomes related to function and pain severity, although more patients discontinued treatment with duloxetine (69). It is noteworthy that this trial recruited non-neuropathic chronic LBP patients, suggesting that the analgesic effect is probably not correlated to the same mechanism(s) in play for DNP pain. Since then, systematic reviews assessing efficacy and/or safety found this drug to be useful for chronic LBP, nonetheless larger studies are recommended to establish definitive evidence in this condition (43,70).

In summary, SNRI's are well established in the treatment of many neuropathic conditions, particularly in DNP. Venlafaxine and duloxetine are the two most used and studied drugs in this class and both present with few adverse effects, better tolerability than TCA's although appear to be somewhat less efficacious than the latter. Conversely both drugs have had promising results in fibromyalgia and conditions with inflammatory components of pain like osteoarthritis and chronic LBP. Dosing is thought to be particularly significant for the analgesic effect and is related to the monoaminergic activity of the drugs. This seems especially true for venlafaxine, while for duloxetine response is seen even in doses as low as 30mg a day.

Table 1 – Main antidepressants used in non-cancerous chronic pain conditions.

Drugs Class	Mechanism of action	Agents	Dose range for pain (mg/24h)	Chronic pain conditions	Adverse events
TCA's					
	5-HT and NE inh. reup. NMDA, ACh, His. antagonism Voltage-gated Na^+ and Ca^{2+} inh. Opioid receptor interaction? Adenosine receptor interaction?	Amitriptyline Clomipramine Imipramine Dosulepin Nortriptyline	10 – 150 10 – 150 10 – 150 25 – 150 10 – 100	DNP; LBP; PHN; PLP; Nerve trauma; Migraines; FM	Sedation; Dry mouth; Drowsiness; Constipation; Weight gain; Hypotension; Prolonged QT interval
SSNRI's					
	5-HT and NE inhibition reuptake	Venlafaxine	75 – 225	DNP; LBP?; Migraines; FM; OA?	Nausea; Insomnia; Drowsiness; Somnolence; Loss of libido
		Duloxetine	30 – 120	DNP; LBP; FM; PHN?; OA	Constipation; Dry mouth; Hyperhidrosis;

5-HT – Setotonine; NE – Norepinephrine; NMDA – N- Methyl- D- Aspartate; ACh – Acetylcholine DNP – Diabetic Neuropathy; LBP – Low Back Pain; PHN – Post-Herpetic Neuralgia; PLP – Phantom Limb Pain; FM – Fibromyalgia; OA – Osteoarthritis

4. Anticonvulsants

Anticonvulsants have been historically used in the treatment of seizures and can be divided into two generations. The first generation of drugs, discovered in the early 20th century include phenytoin, carbamazepine, phenobarbital and valproic acid. Second generation drugs were developed in the 1950's up until today and include older drugs like gabapentin and oxcarbazepine and more recently pregabalin, topiramate, lamotrigine and perampanel (71). The rationale for anticonvulsants administration in chronic pain conditions stems from the fact that they all modulate central and peripheral neuronal transmission via different mechanisms. Presented below is an outline of the main anticonvulsants used to treat chronic pain (Table 2).

4.1 Gabapentinoids

The name of the class is a reference to the chemical related structure of the two drugs, gabapentin and pregabalin, in relation to γ-aminobutyric acid (GABA). Indeed, Gabapentinoids actions are not well understood, yet interactions with sodium, potassium and calcium receptors have been explored. Despite structural similarities to GABA, gabapentinoids do not bind to its receptors nor they interfere with metabolism or transport of this neurotransmitter. Instead, these molecules are ligands to the $\alpha_2\delta$ subunit of voltage dependent calcium channels (L-type mostly), possibly interfering with calcium intracellular accumulation and respective neurotransmitter release (72,73). In addition, thrombospondin, a protein produced by astrocytes and upregulated in nerve injury is known to bind to $\alpha_2\delta_1$ isoform and induce excitatory synaptogenesis contributing to the development of neuropathic pain. High affinity to this isoform of $\alpha_2\delta$ subunit is crucial for the analgesic effect of gabapentinoids that was found to inhibit formation of these excitatory synapses (74). Furthermore, $\alpha_2\delta_1$ also is shown to increase pre and post synaptic NMDA receptor upregulation and activity. Gabapentin binding to $\alpha_2\delta_1$ prevents NMDA receptor expression and normalizes its activity (75).

Since its release in the early 90's, gabapentin showed significant pain relief from case reports in several neuropathic pain conditions such as PHN, DNP, phantom limb pain, post-stroke central pain and spinal cord injury pain, with no major adverse effects reported using titration methods from 300mg/twice or three times a day to 2400mg/day (76,77). Subsequently, larger randomized trials were designed to establish this therapeutic effect. In a large randomized, double-blind trial by the Neuropathic Pain Study Group, gabapentin was tested against placebo in a variety of neuropathic conditions where participants were enrolled if they had at least two symptoms of a list of four (allodynia, burning pain, shooting pain or hyperalgesia). From a sample of 355 patients over an 8-week follow-up period, efficacy outcomes of daily average pain and secondary outcomes

related to quality of life and symptom relief were recorded. Doses were titrated from 900mg/daily up to 2400mg. Gabapentin was shown to relieve pain (primary outcome), and although statistically significant compared to placebo it was a modest result. In secondary outcomes, gabapentin was also found to improve overall condition and quality of life (78). Regarding central neuropathic pain in patients with spinal cord injury, gabapentin was found to be ineffective (79). PHN, for which gabapentin is recommended as first line approach, worsens at night, and disrupts sleep, which in turn diminishes tolerance to pain (22,80). Moreover, it interferes with daily activity and function thereby reducing quality of life. Gabapentin is known for improving quality of sleep and its impact was examined using regression analyses of patients with PHN. Gabapentin was found to improve sleep quality, reduce pain intensity, and improve patient global satisfaction. In addition, sleep quality and pain intensity were found to be independent predictors of patient global satisfaction, which means that even if pain does not subside with gabapentin, patients can still achieve improvements in many pain-related functional impairments (81). Other forms of chronic pain do not seem to respond to gabapentin, like pelvic pain and muscle pain, even when a neuropathic component is involved (82,83). Gabapentin is also studied in combined protocols. Concomitant morphine and gabapentin were found to reduce mean daily pain in lower doses of each drug compared to monotherapy of both drugs and active placebo in DNP and PHN, although an increased risk of respiratory depression has been found when combining the two agents (84,85). Adverse effects reported by numerous trials are very consistent being dizziness, sedation, gait disturbances and visual blurring the most common with a clear dose-response relationship. Further, the therapeutic effect is believed to depend on continuous administration, starting at lower doses and titrate until pain relief occurs and/or tolerability decreases. According to a 2017 review, gabapentin provides moderate pain relief in PHN and DNP (NNT between 5 and 7) in some patients, while others may experience little relief, with limited evidence for other forms of neuropathic pain (86).

Pregabalin is an alkylated analogue of GABA which binds to the $\alpha_2\delta_1$ subunit revealing similar action to gabapentin but unlike the latter, demonstrates linear pharmacokinetic profile (87). Several large, randomized trials were conducted in the beginning of the century establishing robust evidence in favor of pregabalin for DNP and central neuropathic pain resulting from spinal cord injury in doses ranging from 300mg/day to 600mg/day. These trials also measured secondary outcomes related to functional improvement, sleep quality and patient satisfaction showing superiority to placebo in all of them (88–90). Regarding PHN, pregabalin significantly reduces pain intensity in doses of 300mg/day to 600mg/day on large clinical trials of 12 weeks and large samples (91,92). Other forms of neuropathic pain were targeted in randomized trials like post traumatic neuropathic pain and radiotherapy-related neuropathic pain in head and neck cancer patients, with promising results in pain scores, sleep, and overall improvement in quality of life

(93,94). Fibromyalgia was found to respond to pregabalin as well as chronic LBP which as nociceptive and neuropathic components also responds to pregabalin monotherapy although pain scores are even better when combined with celecoxib (95,96). Reported adverse events and tolerability profile was comparable to gabapentin. Overall, pregabalin is very similar to gabapentin in relation to pain relief in DNP and PHN. Other forms of neuropathic pain have limited evidence albeit pregabalin showed interesting results in some of these conditions. No recommendations are made for LBP and fibromyalgia despite pregabalin being used "off-label" in these conditions (97). Effective dose is between 300mg/day and 600mg/day which is the range used by most studies. Indeed, in a 2010 study, doses between 150mg/day to 300mg/day used to assess efficacy of pregabalin in PHN were shown to be ineffective, although the trial was underpowered (little sample size), with a period of only 3 weeks, and patients were allowed to take opioids and NSAID's with no mention of any method to control these confounders (98).

4.2 Dibenzazepines

Dibenzazepines are a class of drugs that act by inhibiting Na^+ currents. Electrophysiological studies in neuronal models show that carbamazepine blocks sustained repetitive firing of action potentials at high frequency of voltage gated Na^+ channels in depolarization states. This neuronal activity pattern is usually seen in epileptic seizures therefore carbamazepine exhibits anticonvulsant action (99). Moreover, carbamazepine and its active metabolite carbamazepine 10,11-epoxide have high affinity for inactivated Na^+ channels, especially channels which have fast inactivation (100,101). This is also true for oxcarbazepine, the ketone analogue of carbamazepine. In contrast, eslicarbazepine acetate a more recent addition to this drug class, reveals preference for slow inactivated state. Slow inactivation state is associated with availability of channels for depolarization; hence this aspect determines the capacity to generate repetitive firing mentioned previously (101,102). This may explain why some patients non-responsive to carbamazepine or oxcarbazepine, respond to eslicarbazepine acetate. Other mechanisms have been proposed such as enhanced K^+ currents and inhibition of voltage dependent calcium channels, all of which may contribute to the neuronal stabilizing effect of these drugs (103,104). Like gabapentinoids, dibenzazepines enhance neuromodulation (figure 3).

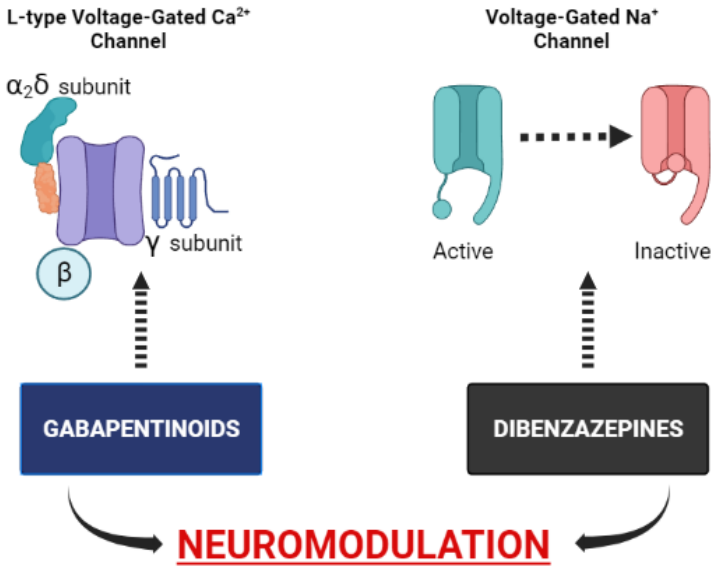

Figure 3 - Main anticonvulsant groups used in chronic pain and their main target receptors. Gabapentinoids bind to the $\alpha_2\delta$ subunit. Dibenzazepines bind with high affinity to inactive Na^+ channels.

Carbamazepine and oxcarbazepine were studied in various types of neuropathic pain. In a novel approach design, Harke et al. tested carbamazepine 600mg/day and morphine 90mg/day in patients with spinal cord stimulation devices which were turned off to simulate a sensitized state. Identified neuropathies were, radicular pain, PHN, DNP, phantom limb pain and complex regional pain syndrome. Results indicated a significant effect of carbamazepine delaying pain generation whereas morphine exhibited only a tendency for pain relief. Authors also note that 600mg/day might be the low threshold and for a more robust analgesia, doses should be increased beyond this level while monitoring for side effects (105). Another study tried to determine the prophylactic effect of carbamazepine in spinal cord injury. Enrolled patients sustained a spinal cord injury within two weeks before selection and were allocated to carbamazepine or placebo group in a blinded fashion. Carbamazepine was titrated during 3 weeks at 200mg/day in each week. Intervention had a 4-week duration with a maximum dose of 600mg/day in the fourth week at which point, carbamazepine dose was slowly decreased and discontinued. Pain prevention was achieved at one month follow-up but not at subsequent follow-ups which took place in three months and six months after the intervention ended (106). Given that the drug was discontinued after one month these results are hardly surprising and further strengthens the evidence for analgesic effect of carbamazepine. Since the early 60's that carbamazepine has been used to treat TN with different studies reporting excellent pain control (>50%pain relief) in more than 60% of patients, even at long term treatments with doses ranging from 100mg to 2400mg (107,108). TN is difficult to control and is usually associated with poor response and sudden symptom outbursts of spasms or seizures,

known as paroxysms. According to the American Academy of Neurology and the European Federation of Neurological Societies, not only does trigger-evoked pain shown a robust response (NNT of 1.8), but also painful paroxysms were reduced in intensity and frequency with carbamazepine. This prompted the recommendation of carbamazepine as the first line treatment for TN by these organizations in issued guidelines (109). Carbamazepine is considered safe and well tolerated with minor adverse events reported such as dizziness, ataxia, sedation, nausea, and headache. An important adverse event of the drug class is hyponatremia, although this may not be clinically relevant unless in cases of concomitant administration with other medications used in elderly people. In the last two decades oxcarbazepine and eslicarbazepine have been gaining traction in the treatment of various neuropathic conditions, due to their more favorable safety profile and tolerability especially in long term treatments (110). In a large multicenter randomized trial, 146 patients with DNP were given oxcarbazepine and placebo for 18 weeks. Oxcarbazepine dose started at 300mg/day and was titrated up to 1800mg/day for 4 weeks. Pain scores after 12 weeks after titration were recorded and ITT analysis was performed. Withdrawals prior to week 16 had their average pain scores from last week carried forward (LOCF) before they withdrew. Authors concluded that oxcarbazepine patients had a >50% pain reduction in 35% of patients compared to 18% in placebo arm and a >30% pain reduction in almost 46% of patient's vs 29% in placebo with a total NNT of 6. Although modest, the results were significant and secondary variables like patient assessment of therapeutic affect were also favorable to oxcarbazepine with 48% of patients mentioning a "very much improved" state while improvements in sleep duration and quality were also reported despite not being statistically significant (111). In another work, oxcarbazepine was tested for efficacy in peripheral neuropathic pain stratified by pain phenotype with doses ranging from 1800 to 2400 mg/day. Patients were randomized according to whether they had sensory profile, like cold, warm and pinprick sensitivity alterations (irritable nociceptor phenotype) or a deafferentation state dominated by sensory loss (non-irritable nociceptor phenotype). The study found a small effect on pain relief and other secondary variables, although there was a significant difference between the two phenotypes, with a much larger response by the irritable nociceptor phenotype (NNT of 3.9 vs NNT of 13). These results give credit to the hypothesis that in the irritable nociceptor phenotype, nerve injury upregulates sodium channels, therefore a sodium channel blocker provides analgesia (112). In TN and PHN, oxcarbazepine as shown efficacy in patients unresponsive to carbamazepine. Onset was rather early with patients reporting pain relief at one week with good tolerability and few adverse effects, establishing the ketone derivate as a suitable alternative (113,114). Eslicarbazepine is the most recent drug of the class with few studies for chronic pain. Most studies are not controlled randomized trials, rather open label, with small sample sizes

which does not allow any meaningful conclusion about its usefulness, albeit results are promising (115).

In conclusion, dibenzazepines are a class of anticonvulsant agents used "off label" in various neuropathic conditions with modest results regarding efficacy except in TN where response is robust. Carbamazepine is first choice for TN and is well tolerated although some patients may be unresponsive or exhibit adverse effects responsible for withdrawals. Carbamazepine also needs a titration period with two or more daily administrations which can lead to poor adherence. Unlike carbamazepine, oxcarbazepine is not metabolized to the 10,11-epoxide metabolite, responsible for most adverse effects of carbamazepine. Oxcarbazepine is better tolerated, patients unresponsive to carbamazepine seem to respond to oxcarbazepine, at least in some conditions and it requires fewer administrations since it has a longer half-life. This makes oxcarbazepine a good alternative to carbamazepine. Eslicarbazepine might be useful, but more evidence is needed before recommendations can be made.

4.3 Other anticonvulsants

Lately, there has been increasing interest in other molecules with anticonvulsant action. Lamotrigine, a sodium channel blocker was employed in two large randomized controlled trials against placebo in DNP. Doses of 200 mg/day, 300 mg/day and 400 mg/day were used in a 12-week maintenance phase with an initial 7-week titration period. Remarkably, 20 to 30% of patients were reported to withdrew before the maintenance phase. Authors reported mixed results with only the 400mg/day dose showing a statistically significant result in pain intensity decrease in one of the trials (study 1). In the other trial a significant effect was detected but only when considering patients who completed the trial, while in post-hoc LOCF analysis, the effect disappears. This is explained by the authors as an underestimation when conducting LOCF imputation since the dropout rate was high as already mentioned (116). In a randomized crossover design study, lamotrigine 400 mg/day did not prove to be efficacious controlling central pain from multiple sclerosis patients, albeit this trial was underpowered due to the small sample size (117). Further randomized controlled trials are needed to corroborate open label studies with positive results for lamotrigine.

Lacosamide, a sodium channel blocker with selectivity for enhancement of the slow inactivation state of the channel and modulation of NMDA receptors, was administered to patients with DNP. Results show a promising effect on this condition and excellent tolerability with very low dropout rate in doses of 400 mg/day. Moreover, the drug has a half-life of 13h, is eliminated unchanged by kidneys in a 95% extension and has minimal biding to plasma proteins which provides

a low potential for displacement of other drugs. This makes lacosamide a good candidate for patients taking other drugs (118,119).

Topiramate is another anticonvulsant with a unique mechanism of action. Besides sodium channel blocking, it also blocks calcium channels, enhances $GABA_A$ receptors and blocks AMPA and Kainate glutamatergic receptors, resulting in excitatory neurotransmission decrease, inhibitory neurotransmission increases and neuron-membrane stabilization (120). Usefulness in neuropathic conditions is poorly established. Topiramate was tested in radicular pain with doses up to 400 mg/day in a placebo crossover randomized trial which did not reach statistical significance in sciatica pain relief. The most important finding was the significant dropout (26%) and adverse events rate with a calculated number need to harm (NNH) of 4.4 with a NNT of 5.3. Authors acknowledge that attrition bias might overestimated treatment effect although they also consider that topiramate may be an option in radicular pain refractory to other first line treatments. Similar results were found in other conditions such as DNP (121). In contrast, topiramate is efficacious in prevention of chronic migraine. A trial conducted in 2007 enrolled 306 subjects and compared topiramate at 100 mg /day with placebo for 16 weeks. Primary outcome was mean monthly migraines and migraine headache days, both significantly reduced by topiramate with good tolerability. These results also translate to meaningful increase in quality-of-life scores (122,123). Since 2019, guidelines of the German Migraine and Headache Society and the German Society of Neurology recognize topiramate as first line for chronic migraine prevention (124).

In 2012, perampanel was approved for the treatment of epilepsy and it is the first AMPA selective, non-competitive antagonist. It is well demonstrated that AMPA receptors are expressed in pre and post synaptic membranes of neurons of the dorsal horn and their activation results in cation influx, membrane depolarization and NMDA activation with subsequent Ca^{2+} influx into the intracellular space. Therefore, the blocking of AMPA receptors leads to neuronal excitability modulation (125). In animal models of neuropathic pain and acute pain with inflammatory component, perampanel has shown significant decreases in pain. Moreover, these studies also demonstrated that the opioid system and the cannabinoid system are probably involved in the antinociceptive effect of perampanel (126–128). A recent case report of a patient with CRPS type I, non-responsive to pregabalin, nortriptyline and tramadol in standard doses, was administered 4mg of perampanel. From the first day onward, the patient improved substantially, while in subsequent follow-up consults, the analgesic effect was retained (129). Perampanel potential use in chronic pain lacks more evidence which should be obtained by well-designed randomized placebo-controlled trials, although early results are very encouraging.

Table 2 – Anticonvulsants used in non-cancerous chronic pain conditions.

Drugs Class	Mechanism of action	Agents	Dose or dose range for pain (mg/24h)	Neuropathic pain conditions					Other chronic pain conditions	Adverse Events
				DNP	PHN	SCI	PLP	TN		
Gabapentinoids										
	$\alpha_2\delta$ subunit of VDCC	Gabapentin	900–2400	+	+	–	?	–	FM?	Dizziness; Sedation; Gait disturbances; Blurred vision. ↑ Respiratory depression risk with opioids
		Pregabalin	300–600	+	+	+	?	–	FM; LBP	
Dibenzazepines										
	VG Na^+ channels inhibition	Carbamazepine	600–2400	+	+	+	?	+	N/A	Dizziness; Ataxia; Sedation; Nausea; Headache; Hyponatremia
		Oxcarbazepine	300 – 2400	+	+	?	?	+		
Other Agents										
	Na^+ channels inhibition	Lamotrigine	400			N/A			DNP?	Dizziness; Headaches; Blurred vision
		Lacosamide	400						DNP?	
	Na^+, Ca^{2+}, AMPA and Kainate inhibition	Topiramate	100			N/A			CMP	Fatigue; Changes in taste; Nervousness; Anorexia; Paresthesia
	AMPA inhibition	Perampanel	4			N/A			CRPS I?	Dizziness; Headaches; Sedation; Nausea

VDCC – Voltage Dependent Calcium Channels; VG – Voltage Gate; AMPA - α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; DNP – Diabetic Neuropathy; PHN – Post-Herpetic Neuralgia; SCI – Spinal Cord Injury; PLP – Phantom Limb Pain; TN- Trigeminal Neuralgia; FM – Fibromyalgia; LBP – Low Back Pain; CMP – Chronic Migraine Prophylaxis; CRPS I – Complex Regional Pain Syndrome type I; N/A – Not Applicable; "+" – At least one RCT supports indication; "-" – No RCT to support indication..

5. Opioids

Opioids have been used by many cultures to alleviate pain and suffering throughout human history. Evidence of efficacy in malignant pain is, according to a Cochrane review ... *"disappointingly low..."*. Nonetheless, it is acknowledged the usefulness of opioids in these patients with most of them having pain relieved in a meaningful way (130). It must be noted that most clinical trials rely on short-term studies of a few dozen weeks or less, with a very small proportion extended to open-label trials. Furthermore, most of these trials focus on analgesic efficacy, function, and patient satisfaction, but no consensus has been achieved for what constitutes the most important therapeutic goal. Considering the complexity of chronic pain, with its different dimensions, conclusions about efficacy of opioids using evidence from an artificial setting with a tendency to select a specific population like clinical trials is challenging. Finally, opioids also bring a particular set of difficulties related to patient behavior like dependence, addiction, and physiological factors such as withdrawal symptoms, induced hyperalgesia and tolerance, all of which will be briefly discussed. Table 3 – **Opioids for non-cancerous chronic pain conditions.** summarizes most common opioids used in chronic pain.

5.1 Endogenous opioid system and physiology

The discovery of opioid receptors has been a consequence of the investigation on inhibitory pathways of the nervous system. Receptors can be of four types, μ (mu), δ delta), κ (kappa), and nociceptin with possibly various subtypes resulting from gene polymorphisms or other processes and all of them are coupled with G-proteins. Endogenous opioid peptides like β-endorphin, enkephalins and dynorphins are natural ligands of these receptors. When activated, opioid receptors inhibit adenylyl cyclase thereby reducing cAMP which results in inhibition of various types of voltage-gated calcium channels and opening of potassium channels (figure 4). Modulation of these ion channels decrease fusion of synaptic vesicles full of excitatory neurotransmitters like substance P and decrease propagation of action potential in second order neurons. In this way, excitatory neurotransmission of nociceptive pain is modulated and inhibited throughout all the neuroaxis where endogenous peptides and opioid receptors are expressed (131). Full opioid agonists are drugs capable of binding to μ receptors with greater affinity, although binding occurs to less extent to other receptors. Most common used full agonists include morphine, codeine, hydrocodone, fentanyl, oxycodone, hydromorphone and methadone and these drugs don't exhibit a ceiling in analgesic effect. Partial agonists like buprenorphine (also considered mixed agonist/antagonist due to antagonism of δ and κ receptors) need to occupy a greater fraction of available receptors for the same analgesic effect seen with full agonists and usually exhibit a ceiling in analgesic effect. While all receptors can mediate analgesia, depending on the type of receptor(s) activated different adverse events are expressed. μ receptors mediate respiratory depression, sedation, nausea, urinary

retention, euphoria, and constipation. δ receptors also mediate euphoria respiratory depression and constipation and, κ receptors exhibit diuretic effects, sedation, and dysphoria. Antagonists were also developed to tackle some of the problems related to opioid use. Naloxone and methylnaltrexone are opioid antagonists used to treat constipation related to treatment refractory to laxatives. Their use does not induce withdrawal symptoms through oral route since they act peripherally and are not systemically absorbed due to first pass metabolism (naloxone) or do not cross the blood-brain barrier (methylnaltrexone). Some approved oral formulations combine opioids with naloxone not only because of side effects in the digestive system but also to avoid tampering with the pills (crushing, chewing, dissolving) to discourage alternative routes of administration such as intranasal or IV (132).

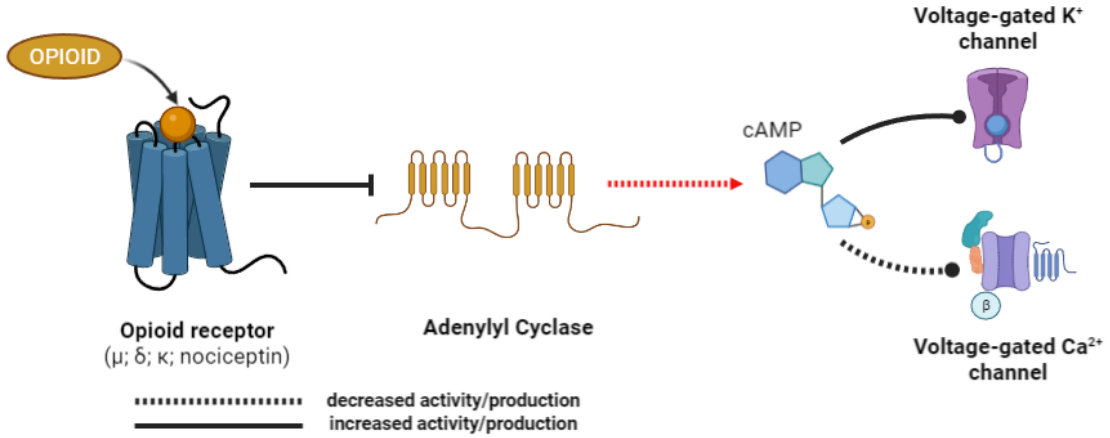

Figure 4 – Activation of the opioid receptor. Receptor activation decreases adenylyl cyclase production of cAMP second messenger, resulting in decreased activity of voltage-gated Ca^{2+} channels and increased activity of K^{+} channels.

5.2 Full μ agonists opioids

Morphine is the prototype for most synthetic and semi-synthetic opioids. Several studies have shown a very significant analgesic effect which prompted interest in evaluating its usefulness in chronic pain management. Some key aspects like responsiveness to opioids, prevailing pain character (nociceptive vs neuropathic), dosing, and careful patient selection, must be addressed before starting an opioid trial. In the 90's, opioids were starting to be considered for chronic pain patients, and trials were conducted to assess it' usefulness in these contexts. A trial in 1992 used morphine administered intravenously, in two doses of 10 and 30mg/ml. It demonstrated efficacy with significant decreases in pain on patients who have tried non-opioid interventions and different

opioid regimens. Even when neuropathic pain was present, half of them responded to the treatment, although the leading notion at the time was that due to its distinct pathophysiological mechanisms, this type of pain did not respond to opioids (133). Similarly, the MONTAS trial demonstrated that patients with neuropathic pain respond very well to opioids (NNT of 1.9), namely morphine. This trial is also important because it was the first one to use as an inclusion criterion, patients who tried a compulsory pretreatment. Included in the study were those with a numerical rating scale (NRS) above 5 (0-10; 0 – no pain; 10 – worst pain) by the end of the pretreatment protocol. Patients undergone a titration period of one week and achieved maximum dosage in the second week of 180mg of morphine, considerably higher than in other trials (up to 120mg) in a double blinded randomized fashion crossover design. Of note, this trial confirms that most patients responded fully or partially according to the definition of the authors of responsiveness and with few adverse events. Other outcomes such as sleep quality, mood and pain disability were significantly improved on those who responded to morphine even if partially(134). In contrast, Khoromi et al. reported no response from lumbar radiculopathy patients to morphine or a combination of morphine and nortriptyline in a randomized blinded crossover four arms (morphine vs nortriptyline vs drug combination vs active placebo) trial. Furthermore, more than half of the patients reported adverse events and dropout rate was considered high. Noteworthy is the fact that this trial included patients with a NRS of 4 and above, meaning that patients included may not have benefited of opioid treatment, simply because their pain wasn't intractable pain. Other important aspect is the dosing in the trial, fairly below others (morphine mean dose alone 62mg/day and 49mg/day in combination) which may not have been sufficient to observe a robust pain relief. Authors also refer that sample size may not have been large enough to detect meaningful differences (135). Another study in patients with chronic osteoarthritis of the hip and knee, underwent an enriched-enrollment withdrawal design, consisting of an open label titration period to effective dose before randomization to placebo or treatment. This design mimics clinical practice where the patient treatment is optimized, dose-wise, before continuing long term treatment. Indeed, this design also comes with drawbacks since exclusion of non-responders does not allow for generalization of results to a large population. Trial duration was 12 weeks in maintenance dose (120mg/day of morphine with possibility of escalation to 160mg/day if needed) with results demonstrating that morphine decreased daily pain significantly and in many secondary outcomes morphine was also favored over placebo (136). Oxycodone is a semi-synthetic opioid with a 1,5 oral morphine equianalgesic dose ratio (also known as MME-morphine milligram equivalent). Studies with oxycodone have exhibited analgesic efficacy for neuropathic conditions like PHN, failed back surgery syndrome, DNP, stenosis of the medullary spinal canal and spinal cord injury in controlled randomized trials as well as open label and observational prospective designs. Safety profile was similar in all these studies, with the most common adverse events being sedation,

nausea, and constipation being the latter the only adverse event whose incidence does not decrease with continuance of treatment (137–139). Fentanyl, another full μ agonist synthetic opioid with an MME of 2,4 is used to relieve chronic pain. It is presented in a controlled released patch formulation dosed in mcg/h and it was tested against sustained release oral morphine in a crossover open label multicenter trial in non-naïve opioid patients. Results indicate preference of patients for transdermal fentanyl since better pain control, better QOL scores and mostly less constipation, were observed with fentanyl treatment (140). Codeine is considered a weak opioid since it depends on bioactivation from CYP2D6 enzyme which converts codeine to morphine with an MME of 0,15 hence it is usually combined with other analgesics, namely paracetamol. It was used in short-term post-surgical dental pain with effective results thus increasing interest for chronic pain conditions which spawned clinical trials to test its efficacy and safety int this context. Codeine exhibits mixed results in patients with rheumatic/arthritic conditions. Pain intensity scores slightly favored codeine/paracetamol combination in relation to active comparator paracetamol, and with a robust response when compared in monotherapy against placebo in two different studies. Doses ranged from mean 180mg/daily to 273mg/daily of codeine. Importantly, both studies reported a significant high dropout and adverse events rate in codeine groups, albeit dropout was not entirely explained by adverse events (141,142). In addition, other combinations with paracetamol like tramadol/paracetamol seem to be as effective as codeine/paracetamol with better tolerability profile (143).

5.3 Multi mechanism opioids

Tapentadol is a novel opioid with a dual mechanism of action, capable of binding to opioid μ receptors and to α_2 noradrenergic presynaptic reuptake receptors. Tapentadol exhibits reuptake inhibition of norepinephrine like venlafaxine. This capability is translated into better results in pain with a neuropathic component associated. Indeed, studies have shown that tapentadol with an MME of 0,4 is superior to morphine in neuropathic pain, achieving greater pain relief with doses below equianalgesic dose. Furthermore, it is equally effective in nociceptive pain and compared to morphine, tolerance develops more slowly making it useful in acute and chronic moderate to severe pain (144). Since its release in late 2000's, tapentadol has been extensively studied in open-label and randomized trials. Open-label studies tested efficacy and safety of mostly extended formulations of the drug in patients with LBP and osteoarthritis. Moreover, patients selected ranged from opioid naïve using WHO step I drugs to strong opioids WHO step III drugs. Interestingly, results are favor tapentadol in most of the outcomes selected, namely pain intensity improvement regardless of the nociceptive or neuropathic predominance of pain. When rotating from transdermal buprenorphine or oral oxycodone using equianalgesic doses, pain control and

tolerability was maintained and even improved (145–147). In randomized controlled trials, tapentadol was compared to placebo and active components like full agonists such as oxycodone. Some studies used enriched enrollement trials mimicking clinical practice while others used more traditional designs over periods not extending beyond 12 weeks. Overall, tapentadol exhibited significant pain intensity improvement and a safety profile superior to oxycodone. Most studies highlighted the tolerability and neuropathic pain efficacy of the drug attributing it to its noradrenergic reuptake inhibition (148,149). Doses usually used for tapentadol studies ranged from 50 to 250mg/twice day.

Another drug with a dual mechanism of action is tramadol. It is metabolized mainly by CYP2D6 in a variety of metabolites, all with different affinities to μ, norepinephrine and serotonin receptors. It's reuptake inhibition of serotonin and norepinephrine is probably responsible for analgesic activity in neuropathic pain. Tramadol is a weak μ agonist but some of the metabolites are significantly more potent with higher affinity to opioid receptors than the parent drug. Importantly, tramadol inferior safety and tolerability profile compared to tapentadol may arise from active metabolites capable of inhibition of serotonin reuptake (150). Tramadol proved to be very effective in many pain conditions, especially with a neuropathic component associated. In a double-blind, crossover randomized trial, 45 patients with polyneuropathies presenting pain and allodynia, tramadol was titrated to 200mg/day and when necessary to 400mg/day. Touch-evoked pain, paresthesia and pain intensity were the primary outcomes. All of them were significantly lower in tramadol patients compared to placebo with an NNT of 4.3 for ≥ 50% pain reduction (151). Another trial compared tramadol (200mg/day-400mg/day) to diclofenac (75 – 150mg/day) in patients with osteoarthritis of the hip and/or knee. Tramadol was as effective in relieving pain as diclofenac with incidence of adverse effects slightly higher in tramadol arm vs diclofenac arm but not reaching statistical significance. Authors highlight the fact that rapid titration may lead to discontinuation of treatment early on when adverse effects are more likely to occur (152). Indeed, in another study where tramadol was compared to placebo in spinal cord injury patients with an initial dose of 150mg/day (50mg TID), 43% of patients dropped out of the trial because of adverse events in tramadol arm (153). Both studies reported improvements in sleep quality with tramadol, a significant aspect to be considered when considering long -term treatment of chronic pain conditions. Tolerability to tramadol can thus be achieved by slow titration. Another strategy is combining tramadol with other analgesic agents into a single formulation. In a trial, tramadol 75mg plus paracetamol 650mg fixed dose was compared to placebo in LBP patients not responding to NSAID's. Primary outcome was a ≥ 30% pain relief and secondary outcomes measured QOL and functionality. In all outcomes, tramadol 75mg plus paracetamol 650mg fixed dose was superior to placebo with a predictable safety profile (20% dropout due to adverse events) (154). Since it was released, tramadol has proven

to be a very effective analgesic in many pain conditions. Like other opioids, efficacy on nociceptive pain is indisputable, while in neuropathic pain it as demonstrated good results with less adverse events. All evidence underscores the significance of slow titration to avoid withdrawal from patients. Of note, tramadol is metabolized by CYP2D6, meaning that interactions with drugs like antidepressants are relevant since many chronic pain patients also use these drugs. Further, polymorphisms in CYP2D6 are responsible for the variable response observed to the drug in the population. Poor metabolizers will not respond as well to the drug since opioid analgesic response is mostly due to an active metabolite of tramadol.

5.4 Opioid use in clinical context and recommendations

Currently, long-term use of opioids in any clinical setting may lead to a series of complications related to drug abuse. Patients receiving opioid drugs are bound to develop tolerance, where to obtain the same analgesic effect, the patient must titrate to a higher dose. Physical dependence is another issue that arises in chronic use. It is linked to the concept of withdrawal syndrome and defined as a state of adaptation produced by abrupt cessation, dose reduction, decreased blood level of the drug or administration of an antagonist. In this case, patients exhibit withdrawal syndrome, a set of symptoms and signs related to drug class. In the case of opioids, it is expected that patient's heart and respiratory rate, body temperature, blood pressure and glycemia increases, while also manifesting sleep disorders and decreased caloric intake and body weight. Patients may also refer, extreme fatigue, dizziness, abdominal cramping, anxiety, irritability, or muscle aches. While it is easy to confuse the concept of "dependence" with "addiction", they are not the same. Addiction is not always predictable to occur in patients, unlike the physiological responses mentioned above (155). Addiction is defined by the American Society of Addiction Medicine as *"...a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual's life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences."*(156). This means that addiction encompasses a set of neurobiological interactions believed to be involved in the reward system of the brain and a development of aberrant behavior leading to inappropriate use of the drug, drug-craving, compulsive use and continued use independent of produced harm.

This led to a series of recommendations by the CDC (Center for Disease Control) and EFIC (European Pain Federation) which provide a framework for clinicians to ensure correct use of these drugs in their patients. The two organizations underline the importance of their recommendations despite making clear that they are not prescribing standards, which means clinicians should take into account the unique features of each patient. Interestingly, both guidelines set the maximum dose on 90mg MME (CDC strongly recommends not exceeding 50mg MME) which contrasts with

most of the clinical and open-label trials with strong opioids reaching 120mg MME or more. Regarding opioid initiation, both guidelines recommend using these drugs as an alternative to nonopioid, non-pharmacological treatments and only when it is expected that benefits outweigh the risks (157,158). The EFIC recommendations also include a list of secondary pain syndromes (as defined by ICD-10) in which opioids can be considered. EFIC clearly states that opioids should not be used in primary pain syndromes due to increased endogenous opioid levels in these patients, making them less responsive and more susceptible to opioid induced hyperalgesia (158). In relation to patient information, it is of major importance that expectations be managed, explaining realist goals to patients and care providers. Information about risks associated with opioid use can include explanation of adverse events, potential fatal respiratory depression in case of drug misuse or abuse and driving difficulties in the titration phase. When decision is made to try an opioid, dose selection and titration strategy as well as regular follow-up is mandatory. Patients should be reevaluated every 3 months after establishment of effective treatment (significant pain relief with no major side effects) (157,158). Curiously, CDC recommendations suggest immediate release opioids in chronic pain instead of extended/long-acting release formulations in contradiction to many of the studies demonstrating better adherence and pain control with these formulations (157). EFIC recommendations do not make specific recommendations about formulation, although recognize that extended formulations may carry a higher risk of dependency. Additionally, EFIC recommends opioid rotation if a trial with an opioid fail, since genetic variation in the population heavily influences response to different opioids (158). Both organizations recommend that clinicians develop a discontinuation plan if treatment goals are not met, benefit does not outweigh the harm, drug abuse disorder arises or if patients refuse urine test in case of suspected non-medical use of opioids (157,158). CDC recommendations also suggest tapering down opioids, starting with a 10% decrease in original drug dose per week or even 10% a month for patients that have been taking opioids for years when initiating discontinuation to avoid withdrawal syndrome (157).

In short, opioids are not a final solution to chronic pain given that much like other analgesics discussed previously, present with low quality of evidence of their efficacy, relying on surveys, open-label trials and short- term clinical trials. Moreover, opioids are only effective in selected patients because of various factors such as the nature of pain (nociceptive pain responds better with lower doses), genetic polymorphisms, tolerance to side effects and aspects related to potential drug misuse and abuse. Opioids are usually considered second line drugs deployed only when alternative pharmacologic and non-pharmacologic treatments have been tried and failed to achieve therapeutic goals. Despite this fact, opioids are an important therapeutic arsenal to consider since some patients responding to opioids may maintain an optimal level of pain control.

Table 3 – Opioids for non-cancerous chronic pain conditions.

Opioid mechanism	Agents	Aprox. dose range used in studies/day	Oral morphine mg equivalent (MME)	Main metabolic pathway	Regular adverse events	Guideline recommendations (2nd line)
Full μ agonists						
	Morphine	60–180 mg	1	UGT2B7	↑ respiratory depression; sedation; nausea; constipation; urinary retention; euphoria	NP*; LBP%; NSCP
	Codeine	180–270 mg	0.15	CYP2D6		NP*; LBP%; NSCP
	Oxycodone	25–60 mg	1.5	CYP3A4		NP*; LBP%; NSCP
	Fentanyl transdermal,	25–100 μg/h	2.4	CYP3A4		NP*; LBP%; NSCP
Multi mechanism opioids						
	Tapentadol	100–500 mg	0.4	UGT1A9; UGT2B7	Nausea; sedation; constipation;	DNP§; NSCP
	Tramadol	150–400 mg	0.1	CYP2D6; CYP3A4		NP*; OA#; LBP%

*NP – Neuropathic Pain; LBP – Low Back Pain; NSCP – Non-Specified Chronic Pain; DNP – Diabetic Neuropathy; OA – Osteoarthritis; * Canadian Pain Society Guidelines (2014); % American Academy of Family Physicians Guidelines (2017); § FDA approved in 2012; # American College of Rheumatology/Arthritis Guidelines (2020).*

6. Cannabinoids

Since the turn of the XXI century, cannabinoids have been increasingly gaining traction as analgesic agents. Extracted from plants of the genus *Cannabis* these chemical compounds and their semi-synthetic and synthetic counterparts are capable of binding to specific receptors found throughout the central and peripheral nervous system exhibiting a wide range of physiological effects. Even though currently more accepted by health care professionals as therapeutical drugs, *Cannabis* and cannabinoids face legal and political barriers in many countries due to their potential for abuse, cognitive-behavioral effects and hazards related to smoking the plant, the most common and effective route of administration.

6.1 Cannabinoid system and pharmacology

The expression and activation of specific receptors in the nervous system related to cannabinoids exhibit a variety of physiological effects. Cannabinoids modulate inflammation signals primarily due to expression of CB_2 receptors in immune cells. Activation of these receptors also provide pain modulation demonstrated by reduced allodynia, mechanical and thermal hyperalgesia. Almost absent expression in the central nervous system helps explain why CB_2 receptors when activated do not exhibit psychoactive effects. In contrast CB_1 receptors are mainly expressed in the cortical regions, cerebellum, and basal ganglia with little expression in the brain stem, medulla, and thalamus. It is established that activation of CB_1 receptors affect motor activity and control, memory processing, cognition, and emotions. CB_1 receptors also regulate pain and are responsible for the dysphoria and mood-enhancing effects experienced by users (159,160). The most important endogenous ligand identified is anandamide an arachidonic acid derivative. Anandamide is capable of binding to CB receptors as well as other receptors involved in nociception like vanilloid receptors producing similar effects to △9-tetrahydrocannabinol (THC), one of the most well studied phytocannabinoids. Despite its putative analgesic effects, THC exposure, particularly in the *Cannabis* naïve population may lead to physiological effects previously mentioned due to its high affinity to CB_1 receptors. Furthermore, there is a possibility of adverse events related to substance abuse behavior when using this compound. Another molecule of interest is cannabidiol (CBD), also found in *Cannabis* plants. Potential use in analgesia stems from the fact that this is a CB_2 agonist. Moreover, CBD poorly binds to CB_1 receptors, thus the lacking psychotropic effects of THC. However, CBD is a powerful inhibitor of many CYP450 isoenzymes like, CYP2D6, CYP3A4, CYP2C9 and others, many of which are involved in metabolization of agents used in the management of chronic pain (160). Regarding pharmacokinetics, cannabinoids are extensively metabolized by the liver and when circulation is reached THC and CBD bound to extensively to proteins. This presents major challenges to orally administered commercial products since bioavailability of the drugs are very

low. When delivered directly to blood circulation by inhalation or smoking, peak serum concentrations are rapidly achieved (3-10 minutes for THC). This route of administration is the preferred one for medical and recreational purposes albeit its hazards consequences, especially for the respiratory tract (159).

6.2 Inhaled Cannabis on chronic pain

Most studies conducted over the last two decades focused on vaporization of the cannabinoid's active compounds. Vaporization allows for safe titration with predictable absorption curves while avoiding combustion of the plant which releases tar, pyrroles, and carbon monoxide, deleterious to the respiratory tract. THC is the main component responsible for analgesia since cannabis strains usually contain less than <1% of CBD. It is now accepted that *Cannabis* has a large body of evidence arguing for its efficacy in chronic pain conditions, namely neuropathic pain, despite no consensus have been attained in relation to doses of THC. In a study with a heterogeneous population of neuropathic pain conditions (CRPS type I; spinal cord injury; peripheral neuropathy and others) of 39 patients, two doses of THC (1,29%; 3,53% per weight of plant) *cannabis* were evaluated against placebo and each other in a randomized double blinded crossover fashion. Of note, 1,29% and 3,53% are considered "low" and "medium" doses. Primary outcome was pain intensity, measured on the VAS scale, while secondary outcomes included psychoactive effects, mood, and neurocognitive effects. All participants were either marijuana users or ex-users. Those using at the time of recruitment had to refrain from smoking the plant 30 days prior to treatment sessions. Compliance was assessed with urine tests. Results demonstrated a superior effect of *Cannabis* in relation to placebo although equianalgesic effect between the two doses with a NNT around 3. Regarding secondary outcomes, a significant effect was recorded against placebo with both doses improving descriptors associated with neuropathic pain. Both doses registered psychoactive effects but, in this case, medium dose presented an increased sensation of euphoria when compared to low dose. Cognitive tests did not reveal significant impaired motor control, although learning and memory shown a slight decrease. This may be explained by the fact that enrolled patients were users or ex-users of *Cannabis*, demonstrating developed tolerance. Withdrawals were minimal and were not attributed to tolerability issues. Authors concluded that low dose may be as beneficial as higher doses with a better risk-ratio profile (161). Similarly, 16 patients with DNP were recruited for a short-term randomized double-blinded crossover trial to evaluate the efficacy of three doses of THC (1% ;4% ;7% per weight of plant) in vaporized *Cannabis*. Findings reported a dose dependent analgesic effect with the highest dose obtaining greater pain relief compared to the other doses and all doses obtaining a significant pain relief compared to placebo. All subjects experienced euphoria or somnolence and cognition tests revealed a negative impact

mainly on attention and working memory, albeit no significant differences were detected between high dose and low dose or placebo. It is worth noting that both trials are short-term, psychoactive effects of *Cannabis* were reported in most if not all patients (compromising blindness) and other adverse effects like somnolence and cognitive impairment are likely to occur and maintain for hours after administration (162). Recently, the pharmacokinetic interactions between THC and CBD were studied in a randomized double-blind crossover trial. Patients presented with fibromyalgia and were given three different varieties of *Cannabis* with standard concentrations of THC and CBD ranging from low THC (13,4mg) high CBD (17,8mg) content, residual THC (<1mg) high CBD (18,4mg) content and high THC (22,4mg) residual CBD (<1mg) content. Interestingly, authors found no significant analgesic effects of any of the three varieties when compared to placebo in relation to spontaneous pain scores (primary outcome). Pressure pain results also demonstrated an increase in pain threshold in the two varieties with high THC content, while no analgesic effect was observed with the high CBD content variety. Importantly a major interaction between the two cannabinoid molecules was reported. THC plasma concentrations were at least 50% higher in the two varieties with high CBD content when compared to the CBD residual variety. Some explanations are forwarded by the authors for this phenomenon, like possible enhancement of THC absorption in the lungs by CBD, metabolism inhibition of THC by CBD or conversion of CBD into THC, since they are chemically related (163).

Cannabinoid products for medical use are a promising lane for the treatment of chronic pain, especially when other analgesics have failed. Their interest goes beyond pain relief since a sparing opioid effect seems more evident when using rich-CBD hemp extract (164). Despite disappointing results on rheumatic conditions, cannabinoids are still used by patients with OA and fibromyalgia, probably because of good results in anxiety and sleep (165). THC rich products produce moderate response in neuropathic pain on some patients, but route of administration and inhalation technique are major drawbacks in the case of inhaled *Cannabis* (166). Adverse effects are mild to moderate even in the presence of high concentrations. Euphoria and "high" feeling are the most reported events, along with sedation, dizziness, and cognitive impairment. It has to be taken into account that cannabinoids are potentially addictive, meaning that substance abuse disorder has to be considered similar to opioids. Regulatory aspects and acceptance by healthcare professionals and patients in combination with previously mentioned aspects relegate inhaled *Cannabis* to an alternative treatment only when other conventional analgesics do not work.

7. Conclusion

Chronic pain embarks a multitude of physiological, behavioral, and affective components. Approach to chronic pain relies on the combination of different treatment modalities none of which is totally satisfactory. Pharmacotherapy is a key component of this combination providing results that range from mild to moderate relief of pain. Other factors related to chronic pain can be improved with these agents such as sleep, anxiety, depression, and patient satisfaction.

Selected medication depends on the etiology of pain, pain intensity, patient characteristics, drugs safety profile and tolerability. NSAID's are the first line of treatment for osteoarthritis and demonstrated pain relief in other conditions such as LBP. Their usefulness in neuropathic conditions is questionable despite being prescribed as adjuvants. Antidepressants and Anticonvulsants are widely prescribed in patients with neuropathic pain, be it peripheral like DNP or central like in spinal cord injury, with various degrees of tolerance and efficacy. Antidepressants like TCA's are the gold standard for neuropathic conditions albeit their safety profile and tolerance must be considered, especially in the elderly. SNRI's are considered a safer option and display efficacy in fibromyalgia. Most anticonvulsants are approved for neuropathic pain conditions, namely, PHN and DNP also displaying improvements in other comorbidities such as sleep disturbance or physical impairment, which reduces quality of life. Opioids are considered only when other drugs fail or do not achieve necessary pain relief, since their prescription can lead to misuse and abuse. Cannabinoids are a new approach to pain management which has great potential since it can be opioid sparing. These drugs show a moderate effect on neuropathic pain and small effect in rheumatic pain despite improving other factors like sleep and physical function. Nonetheless major hurdles stop the widespread use of *Cannabis* products like route of administration, inhalation technique and the possible tendency to abuse rich THC drugs.

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