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Alternatives to Opioids in the Pharmacologic Management of Chronic Pain Syndromes: A Narrative Review of Randomized, Controlled, and Blinded Clinical Trials

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Abstract

Chronic pain exerts a tremendous burden on individuals and societies. If one views chronic pain as a single disease entity, then it is the most common and costly medical condition. At present, medical professionals who treat patients in chronic pain are recommended to provide comprehensive and multidisciplinary treatments, which may include pharmacotherapy. Many providers employ non-opioid medications to treat chronic pain, however, for some patients, opioid analgesics are the exclusive treatment of chronic pain. However, there is currently an epidemic of opioid use in the United States, and recent guidelines from the Centers for Disease Control (CDC) have recommended that the use of opioids for non-malignant chronic pain be used only in certain circumstances. The goal of this review was to report the current body of evidence-based medicine gained from prospective, randomized-controlled, blinded studies on the use of non-opioid analgesics for the most common non-cancer chronic pain conditions. A total of 9566 studies were obtained during literature searches and 271 of these met inclusion for this review. Overall, while many non-opioid analgesics have been found to be effective in reducing pain for many chronic pain conditions, it is evident that the number of high-quality studies is lacking and the effect sizes noted in many studies is not considered to be clinically significant despite statistical significance. More research is needed to determine effective and mechanisms-based treatments for the chronic pain syndromes discussed in this review. Utilization of rigorous and homogeneous research methodology would likely allow for better consistency and reproducibility, which is of utmost importance in guiding evidence-based care.

Introduction

It is estimated that over 100 million Americans spend each day in chronic pain, at a yearly cost of over $600 billion in lost productivity and health care expenditures[1]. A central theme outlined in a 2011 Institute of Medicine report was that despite the care of chronic pain patients being extremely costly, outcomes continue to remain relatively poor[1]. Currently, physicians who treat patients in chronic pain are advised to provide comprehensive and multidisciplinary treatments. A multidisciplinary pain strategy typically includes physical therapies, psychological care, and pharmacologic management. Pharmacologic therapies are typically aimed at treating the underlying pathophysiologic mechanisms or are simply used for symptom-based treatment. Many practitioners rely on non-opioid medications to treat chronic pain, however, for some patients; opioid analgesics are utilized for the symptomatic treatment of chronic pain.

In 2016, the Centers for Disease Control (CDC) published guidelines on the use of opioid analgesics for chronic non-malignant pain, in response to the increasing rates of opioid prescribing coupled with an epidemic of opioid use disorders in the United States[2]. Opioid prescriptions increased per capita by 7.3% from 2007 to 2012, and in 2012 alone, 259 million prescriptions for opioid pain medications were written, enough for every adult in the United States to have a bottle of opioid medications[3,4]. Evidence from the literature supports

short-term efficacy of opioids for reducing pain and improving function in some pain conditions, but there is a paucity of evidence that suggests long-term benefits of opioids for chronic pain[5].

The first recommendation of the CDC guidelines is that non-pharmacologic and non-opioid pharmacologic therapy are preferred for chronic pain and should be tried first[2]. Non-opioid pharmacotherapy includes, but is not limited to: acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), amine reuptake inhibitors (ARIs), and membrane stabilizers. The goals of this review are to provide the reader with data from prospective, randomized, controlled, and blinded clinical trials where non-opioid medications were investigated for the treatment of chronic pain.

Methods

Inclusion Criteria

Studies eligible for this review had inclusion criteria of adults (≥18 years) with pain syndromes of chronic duration (≥3 months) including: chronic low back pain (CLBP), myofascial pain syndrome (MPS), fibromyalgia (FM), post-herpetic neuralgia (PHN), painful diabetic neuropathy (PDN), radicular pain (RP), and complex regional pain syndrome (CRPS) (Table 1). These conditions were chosen for this review as they represent the most common chronic pain syndromes that current pain management physicians treat. Studies must have investigated the efficacy of non-opioid medications (Table 1) compared to placebo or another medication using a prospective, randomized, controlled, and a blinded design (designated as PC-RCT). Studies were excluded unless the type of blinding used was explicitly stated in the prose of the manuscript. Studies were included if their primary outcomes were the impact of the non-opioid pharmacotherapy on pain severity (including: change in pain score from baseline, functional status, or proportion of patients with response).

Literature Search

To identify relevant articles, literature searches were conducted in Medline (PubMed), Cochrane Library, and Scopus with no limitation on the year of publication. The database searches were performed from March to May, 2017. An exhaustive search strategy including a base search term for the chronic pain condition coupled with a changing search term for the non-opioid medication investigated was employed. The search strategy and terms are provided in Supplemental Appendix 1. Searches were limited to human species and the English language. Filters such as “clinical trial” or “randomized clinical trial” provided by the search engines were not used; the decision to designate as a PC-RCT was that of the authors after review of the study methodology. The reference sections of original studies, meta-analyses, systematic reviews, or evidence-based recommendations were manually screened independently by the authors for additional articles.

Study Selection & Data Abstraction

All authors independently screened each title and abstract for potential full-text review based on the aforementioned inclusion criteria. Disagreements were resolved through discussion

and consensus. After the full-text of the studies was retrieved, each was again independently screened for eligibility by all authors, with disagreements resolved through consensus to arrive at the final set of included studies. Data extraction was carried out independently by all authors, using a standardized extraction form. Characteristics of the selected studies included: methods, participants, intervention, and outcomes were recorded on the standardized extraction form.

Results

The literature searches revealed a total of 9566 citations. 7098 citations were excluded due to being unrelated or duplicate. 2468 citations were screened and 2197 excluded for the following reasons: review articles (narrative or systematic), meta-analyses, case reports/series, observational studies, retrospective studies, non-randomized studies, non-blinded studies, acute pain population, non-pain efficacy primary outcome, publication is a protocol for an upcoming trial, or studies that did not have a control arm (either placebo or active comparator). The final number of studies included were 271 studies investigating the efficacy of non-opioid analgesics on chronic pain syndromes (Supplemental Figures 1–7).

Findings from Studies Grouped by Chronic Pain Syndrome

Chronic Low Back Pain (CLBP)

Chronic low back pain (CLBP) is one of the most commonly encountered conditions in clinical practice. Despite its prevalence, it is a condition that leads to high medical utilization and disability and, unfortunately, there are few effective interventions[6]. The treatment of CLBP includes the use of prescription medications such as acetaminophen, NSAIDs, ARIs, membrane stabilizers, and other miscellaneous non-opioids or opioids. Despite the fact that CLBP is the second most common reason that symptomatically drives people to see their physicians, there are no on-label FDA approved medications for this condition. The treatment of CLBP includes the use of a variety of prescription medications that do not have FDA approval for CLBP (Table 2).

Acetaminophen—Only two randomized, active-comparator controlled, double-blind trials met criteria for inclusion into this review[7,8]. In the study by Bedaiwi et al[7], 50 patients with CLBP were randomized to either acetaminophen (500 mg twice daily) or celecoxib (200 mg twice daily) for 4 weeks[7]. After treatment, patients randomized to celecoxib had a 2 point reduction in their pain scores compared to a 0.5 point reduction in the acetaminophen group. Hickey enrolled a total of 30 patients into a study comparing diflusinal (500 mg twice daily) with acetaminophen (1000 mg four times daily) and found that diflusinal was superior in reducing pain scores compared to acetaminophen[8].

NSAIDs—Seven studies investigating oral NSAIDs for the treatment of CLBP met inclusion criteria[9–15]. Five studies found NSAIDs to be superior to placebo for CLBP for naproxen[9], etoricoxib[10,13], valdecoxib[11], and rofecoxib[12]. In the study by Berry et al, diflunisal was not found to be superior to placebo for CLBP[9]. Two studies investigated the effect of an NSAID compared to an active NSAID comparator on pain relief – both of these

studies demonstrated efficacy of the study drugs as well as non-inferiority of either celecoxib compared to diclofenac[15] or piroxicam compared to indomethacin[14].

ARIs—There were a total of 13 studies evaluating the efficacy of antidepressants for CLBP. These included 5 studies on tricyclic antidepressants (TCAs) and 8 studies on selective norepinephrine or serotonin reuptake inhibitors (SNRIs and SSRIs). Ward et al investigated comparative effectiveness of doxepin to desipramine in two separate studies[16,17] and found that both doxepin and desipramine are effective in the treatment of CLBP and in one of the studies found doxepin to be superior[16]. Atkinson et al found that nortriptyline was superior to placebo for pain relief[18] and that low-dose desipramine provided superior relief of pain compared to placebo, high-dose desipramine, and fluoxetine comparison groups[19]. Imipramine was not found to be statistically superior to placebo in the treatment of CLBP in a study of 60 patients[20]. Duloxetine, an SNRI, has been studied in 5 RCT studies for the treatment of CLBP and was found to be superior to placebo in 4 out of 5 of them at the endpoint of the study[21–24]. The one negative study had statistically significant improvements in pain ratings at all time-points except at the final assessment[25]. Maprotiline, an SNRI, was found to be superior to paroxetine and active placebo (diphenhydramine) in 103 patients with CLBP at 8 weeks[26]. SSRIs paroxetine and bupropion have not been shown to be superior to placebo for treatment of CLBP[27,28].

Membrane Stabilizers—Few studies have looked at the use of the anticonvulsant drug class on CLBP. One study by Atkinson et al investigated gabapentin versus inert placebo for CLBP and found that within each treatment arm, there was statistically significant reductions in pain, but when comparing gabapentin to placebo, there was no statistically significant difference in pain relief between the two groups[29]. Two studies have investigated pregabalin compared to active control groups and pregabalin was not found to be superior to opioids[30] or celecoxib[31] for treatment of CLBP, however celecoxib plus pregabalin was superior to monotherapy in the study by Romano et al[31]. Muehlbacher et al studied the effects of topiramate on CLBP compared to inert placebo and showed that topiramate was superior to placebo in reducing pain scores[32].

Muscle relaxants—The majority of randomized controlled trials evaluating the use of muscle relaxants for CLBP were studied in an acute pain setting instead of a chronic pain population, and after exhaustive searching, only 3 studies met the inclusion criteria. In a study by Baratta et al, 105 patients with CLBP were randomized to either carisoprodol, propoxyphene, or placebo for 14 days and results showed that carisoprodol was significantly better than placebo in relief of pain, but there was no statistical difference between the improvement seen with carisoprodol versus propoxyphene[33]. In a study by Brown et al, 49 patients with chronic spine pain were randomized to cyclobenzaprine, diazepam, or placebo for two weeks[34]. Results showed that patients receiving cyclobenzaprine or diazepam had superior pain relief compared to placebo group, however, there was no difference in the pain response between the cyclobenzaprine or diazepam groups. Additionally, Basmajian reported no difference in short-term reduction of pain and muscle spasms in CLBP patients between cyclobenzaprine and placebo after 18 days[35].

Mixed ARI / Opioid—Although tramadol and tapentadol have some activity at the *mu*-opioid receptor, they also work via norepinephrine and serotonin reuptake inhibition and thus are included in this review. A total of 12 studies met inclusion criteria. Six studies found that tramadol, tramadol/acetaminophen, or tapentadol had superior efficacy for the treatment of CLBP compared to placebo[36–41]. Schiphorst Preuper et al found that tramadol/acetaminophen was not superior to placebo for CLBP[42]. In a study comparing celecoxib to tramadol, O'Donnell et al published that celecoxib 200 mg bid was superior to tramadol 50 mg qid in the relief of CLBP[43]. Four studies comparing tramadol, tramadol/acetaminophen, or tapentadol to an active comparator showed superiority in pain relief over the control group (oxycodone[44], study drug plus pregabalin[45], codeine/acetaminophen[46], and NSAIDs[47]).

Topical lidocaine patch—A study by Hashmi et al randomized 30 patients to either a 5% lidocaine patch or placebo patch[48]. After 2 weeks of use, both lidocaine and placebo patch groups reported a greater than 50% decrease in pain, suggesting that there may be no independent efficacy of 5% lidocaine patch for CLBP, but there is also a large and significant placebo effect, and that 5% lidocaine patch is not statistically significantly superior to placebo.

Topical capsaicin—One study met inclusion criteria and found that capsaicin cream was superior based on pain relief (at least a 30% reduction in numerical pain score rating) to placebo cream in 154 patients over 3 weeks[49].

Botulinum toxin type A (BoNT-A)—A study by Foster et al involving 31 patients with CLBP being treated with BoNT-A met criteria for inclusion[50]. In this study, 15 patients received 200 units BoNT-A in the lumbar spine paraspinal muscles and 16 received normal saline injection. Those who received BoNT-A injections had superior pain relief compared to saline injections at 3 and 8 weeks after treatment.

N-methyl-D-aspartate (NMDA) antagonists—In a study by Kleinböhl et al, it was found that in patients who received 100mg of amantadine, an NMDA antagonist, compared to placebo over one week had no difference in pain rating scores at the end of the treatment period[51].

Miscellaneous—Tanezumab, a monoclonal antibody against nerve growth factor, is given intravenously and has been investigated in two different studies. Both studies evaluated the efficacy of tanezumab against naproxen and placebo. Both studies reported that tanezumab was superior to naproxen and placebo at both a 6-week pain outcome endpoint[52] and a 16-week pain outcome endpoint[53].

Myofascial Pain Syndrome (MPS)

Myofascial pain syndrome (MPS) is a common painful condition encountered in the general population. It is a localized muscle condition that presents with skeletal muscle pain and stiffness[54]. Classically, it is defined by the presence of trigger points in specific musculature. The exact pathophysiology and etiology of myofascial trigger points and myofascial pain

syndrome is still unknown. Despite MPS being quite common, they are most often under-diagnosed or misdiagnosed conditions. The treatment of MPS includes the use of prescription medications, however, no medications are specifically FDA-approved for MPS, although many muscle relaxants have indications for muscle spasm. The treatment of MPS includes the use of a variety of prescription medications that do not have FDA approval for MPS (Table 3).

NSAIDs—Two studies were identified using injected or topical NSAIDs that met inclusion criteria. Frost investigated the efficacy of diclofenac trigger point injections versus lidocaine injections for chronic localized myofascial pain. This study found that in the short-term (5 hour follow-up period), diclofenac injections produced a significant improvement in pain score compared to lidocaine at 4 hours[55]. Hsieh et al found that diclofenac sodium patch (60mg) provided significantly superior pain relief compared to control patch after 8 days in patients with chronic myofascial pain of the upper trapezius muscle[56]. No studies evaluating oral NSAIDs for chronic myofascial pain met criteria for inclusion.

ARIs—One study met inclusion criteria and studied the efficacy of fluoxetine versus amitriptyline for musculoskeletal pain. Schreiber et al randomized 40 patients to either amitriptyline (50–75 mg/day) or fluoxetine (20 mg/day) for six weeks[57]. The degree of pain relief within each treatment group was moderate to good at the end of the study, however, the difference in responses between drugs was not statistically significant.

Muscle Relaxants—The majority of published studies evaluating the use of muscle relaxants for MPS were either studied in an acute pain setting instead of a chronic pain population or did not meet other inclusion criteria, and after exhaustive searching, only 1 study met the inclusion criteria. In a study by Valtonen et al, 118 patients were either placed on methocarbamol 1500 mg qid or placebo for one week[58]. After one week of treatment, there was a statistically significant superiority of patients having effective pain relief compared to placebo.

Topical lidocaine patch—A study by Affaitati et al was included in this review and compared the effects of a topical lidocaine patch (total daily dose 350 mg), placebo patch, and injection of 0.5% bupivacaine over one painful trigger point for a total of 4 days[59]. This study found that lidocaine patches and local anesthetic infiltration were effective for pain and superior to placebo in the short-term for patients with MPS. Another study by Lin et al reported that 5% lidocaine patch used for 14 days in cervical myofascial pain syndrome may be superior to placebo, but the significant difference between the two groups may have been skewed by an unexpected increase in pain in the placebo patch group[60].

Topical capsaicin—Two studies were found to meet inclusion criteria investigating capsaicin patch for MPS – one compared efficacy to placebo patch[61], and the other compared to NSAID patch, NSAID patch plus transcutaneous electric nerve stimulation (TENS), and placebo[62]. Neither study found that capsaicin patch provided superior pain control when analyzed to the comparator group.

BoNT-A—The majority of available studies that met criteria for inclusion for MPS are in the study of BoNT-A for pain. All but one of the included studies investigated patients with cervical and shoulder girdle MPS and the majority utilized a placebo or control procedure. The sole study looking at lumbar MPS was performed by De Andres et al and found that BoNT-A was not superior in efficacy to placebo, but was efficacious in a within group analysis[63]. There were seven studies that showed superior efficacy of BoNT-A injections for cervical MPS either compared to saline[64–68], local anesthetic and dry needling[69], or steroid[70]. Eight published studies had negative findings where BoNT-A was not found to have superior efficacy to control procedure, either saline[71–77] or local anesthetic[78]. The discrepancies between positive and negative studies has been postulated to exist due to heterogenous research design methodology and use of control procedures that are thought to produce analgesic benefits of their own[54].

Fibromyalgia (FM)

Fibromyalgia is the second most common “rheumatologic” disorder, second only to osteoarthritis[79]. Depending on the diagnostic criteria used, the prevalence is from 2 to 8% of the general population[79]. Pain in FM is often widespread and can be challenging and difficult to control. The treatment of FM includes the use of a variety of prescription medications that have FDA-approval for FM and those that do not (Table 4).

NSAIDs—Two studies met inclusion criteria for this review. In the study by Yunus et al, 46 patients with FM were randomized to either ibuprofen 600mg qid or matched placebo for a total of 3 weeks. At the end of three weeks, pain rating scores between the two groups did not show superior efficacy for the ibuprofen group compared to the placebo group, nor was there any within-group significant reductions in pain[80]. Russell et al performed a four-arm study investigating ibuprofen + alprazolam, ibuprofen + placebo, alprazolam + placebo, and placebo + placebo in 78 patients for 8 weeks[81]. Their findings indicated that the ibuprofen + alprazolam group had significantly greater reduction than placebo + placebo group. Monotherapy groups appeared to have similar reductions in pain to the combination group, but no statistical analyses were performed.

ARIs—A total of 29 studies were found to meet inclusion criteria and included studies on TCAs, SNRIs, and SSRIs. Milnacipran is a SNRI that is approved by the FDA for the treatment of fibromyalgia and 10 studies met criteria for inclusion in this review. Only one of these studies, by Staud et al had a negative finding between milnacipran and placebo groups, however, statistically significant reductions of small magnitude were noted within groups[82]. 9 studies, many with large sample sizes, showed superior efficacy in pain reduction with milnacipran compared to placebo[83–91]. 12 studies evaluated duloxetine, a SNRI that is approved by the FDA for treatment of fibromyalgia. 9 of these studies demonstrated superior efficacy of duloxetine compared to placebo at varying dosages of the drug, with 60 to 120 mg being the most commonly studied[92–100]. 3 studies reported non-superior efficacy of duloxetine to placebo, one studied a 30 mg dose[101,102], one studied a 60 mg dose, and one studied either 60 or 120 mg dose[103].

6 studies investigated the efficacy of TCAs for the relief of pain in FM. 4 studies showed efficacy of the TCA amitriptyline that was superior to placebo[104–107]. In a study by Heymann et al[108], they investigated amitriptyline and nortriptyline compared to placebo and although there was reduction in pain noted with both TCAs, it was not statistically significantly different than placebo. In the study by Carette et al, amitriptyline was not superior to placebo, but had significant within group reduction in pain scores[109].

Very few RCT studies have investigated the impact of SSRIs on pain in FM. Fluoxetine, a SSRI was investigated in a study by Goldenberg et al and was found to be superior to placebo when used in monotherapy or combined with amitriptyline[105]. Controlled-release paroxetine has been investigated in a study by Patkar et al, and their findings indicate that it is superior to placebo for pain relief after 12 weeks of treatment in 116 patients[110].

Membrane Stabilizers—A total of 8 studies have been reported for pregabalin that met criteria for this review. 7 of these studies investigated pregabalin monotherapy at varying doses ranging from 150–600 mg/day and were found to have superior pain relief compared to placebo. Arnold et al[111] and Mease et al[112] both found that daily total doses of 300/450/600 mg were all superior in pain efficacy to placebo. Crofford et al found that only 450 mg/day dosing was superior to placebo for pain efficacy (not at 150 or 300 mg/day)[113]. At doses of 300 or 450 mg/day, Ohta et al reported superior efficacy of pregabalin over placebo[114]. Arnold et al[115] and Clair[116] et al also reported superior efficacy of pregabalin in pooled groups of pregabalin doses (300–450 mg/day) over placebo. Pauer et al published that only a modest statistically significant effect over placebo was noted at 450 mg/day (not at 300 or 600 mg/day)[117]. In a study by Gilron et al, combination therapy of pregabalin + duloxetine versus placebo or monotherapy was investigated and the authors reported that combination therapy is superior to placebo and pregabalin monotherapy[118].

Only one RCT investigating gabapentin was identified that met inclusion criteria. In this study by Arnold et al, 150 patients were randomized to either placebo or gabapentin (titrated to doses of 1,200–2,400 mg/day) for 12 weeks[119]. Results showed that gabapentin treated patients had significantly greater improvement in average pain scores of a modest effect.

Muscle relaxants—Three studies regarding the use of cyclobenzaprine in the treatment of FM pain met inclusion criteria. Two of these showed superior efficacy for relief of pain over placebo[120,121], however in the Quimby et al study, the authors noted a significant bias in blinding in that due to side effects of the drug, they knew that they were getting the study drug and not placebo[120]. Reynolds et al published a report showing that cyclobenzaprine was not superior to placebo in the treatment of FM pain[122].

In a study by Vaeroy et al, a combination analgesic containing carisoprodol/caffeine/acetaminophen was compared to placebo for pain in FM in 58 female patients with FM over 8 weeks[123]. No between-group comparisons are reported in the manuscript, however, there were statistically significant improvements within both treatment groups.

Mixed ARI / Opioid—Only one study met our strict inclusion criteria by Bennett et al[124]. In this study, the efficacy of tramadol/acetaminophen (up to a total dose of 300 mg tramadol/

2600 mg acetaminophen per day) was compared with placebo in a total of 315 patients enrolled in the study which lasted approximately 3 months. The authors reported that tramadol/acetaminophen significantly reduced pain severity compared to placebo at study end.

NMDA antagonists—In a study by Noppers et al, 24 FM patients were randomized to either a 30 minute infusion of ketamine (total dose 0.5 mg/kg) or active comparator midazolam (total dose 5 mg)[125]. The authors reported no significant differences in pain scores between treatment groups at either a 2.5 hour or 8 week follow-up time point, however, statistically significant differences were noted for within-group analyses for both treatments.

Olivan-Blázquez et al performed a study in 63 FM patients and randomized to either memantine, an NMDA-receptor antagonist, at the dose of 20 mg daily for 6 months or placebo[126]. Compared to placebo, memantine significantly reduced pain score ratings at the end of the study period.

Opioid antagonists—In the sole study that met inclusion criteria, Younger et al performed a randomized crossover placebo-controlled study where 31 women with FM were placed on either oral low-dose naltrexone (4.5 mg/day) or placebo and followed for 16 weeks[127]. At the end of the study, there was a significantly greater reduction in pain in the low-dose naltrexone group compared to those taking placebo.

Local anesthetics—Three studies met inclusion criteria and found that infusions of 240 mg of IV lidocaine once a week for 4 weeks, in patients with FM all taking amitriptyline, did not provide superior efficacy for pain relief compared to patients receiving placebo infusions[128–130].

Steroids—In a study by Clark et al, 20 patients were randomized into a double-blind, crossover study investigating the efficacy of prednisone versus placebo for FM pain – each treatment was studied for 14 days[131]. There was no improvement seen in patients taking prednisone versus placebo and in fact, pain worsened with prednisone treatment over time.

Cannabinoids—Skrabek at al performed the one study on a cannabinoid for FM pain that met inclusion criteria[132]. In this study, 40 patients were randomized to receive oral nabilone, a cannabinoid-1 receptor agonist, versus oral placebo. Findings from this study show statistically significant reductions in pain score at 4 weeks in patients taking nabilone versus placebo.

Post-herpetic neuralgia (PHN)

PHN develops after the reactivation of the herpes zoster virus (HZ) from its latent state. The incidence of HZ reactivation in the United States is around 500,000 cases per year or approximately 2 cases per 1000 persons. Patients over 70 years of age with HZ have a 50% risk of developing PHN whereas patients under 40 years of age rarely develop it[133]. The treatment of PHN includes the use of prescription medications that have FDA-approval for PHN management and those that do not (Table 5).

Membrane Stabilizers—Pregabalin was found to reduce 'worst possible' pain intensity within 2 days of treatment inception and remained significant throughout two 8-week multicenter randomized placebo controlled trial (PC-RCT)[134,135] and other trials[136,137]. It also reduced sleep interference[134,135,137], improved general health satisfaction[134], health related quality of life[135,136], improved mood[135–137], and was associated with a significant impression of improvement assessed by the patient[134–137] and clinician[134,135]. Fifty percent of patients with baseline pain intensity had >50% relief compared to 20% in the placebo group over the study period RCT yielding a number needed to treat (NNT) of 3.4[134]; similar percentages were observed in a subsequent PC-RCT yielding a NNT of 3.6[138]. The pain reduction occurs within 1.5–3.5 days[136]. The minimal effective dose ranged from 150 – 200 mg/daily[134–136] and the effect is dose dependent to 600mg[134–136,138].

Gabapentin has been shown to be effective in the reduction of pain intensity[139,140], improvement in sleep interference[139,140], quality of life[139,140], mood[139,140], patient[139] and clinician[139] reported improvement in pain in PC-RCTs. The pain reduction occurs within 1[140] or 2[139] weeks and the NNT was 3.2[139]. Similar results have been recorded in PC-RCTs in Canada[141,142], however these trials combined multiple neuropathic pain conditions including PHN. The minimal effective dose was 1800 mg/daily[140]. The gabapentin pro-drug (gabapentin encarbil, Pd-G) had a significant reduction in averaged 24 hour pain scores compared with placebo[143] The minimum effective dosage was 1200mg/daily. Single daily administration of gastro-retentive gabapentin (Gr-G) was more effective than placebo in one study[144] but the same study found no difference when given twice daily[145]. The data is further challenged as a 3rd trial found no benefit from single daily dose Gr-G but did find benefit from twice daily dosing[146].

The efficacy of oxcarbazepine has been examined in neuropathic pain conditions, however the sample size of the PHN sub-group was insufficient to make conclusions[147]. The efficacy of levetiracetam has been examined in a small RCT with encouraging results, but the pilot study has never been replicated in a larger population[148].

ARIs—The TCAs nortriptyline[149], desipramine[150,151], and amitriptyline[151,152], have been shown to be effective in the reduction of pain intensity and improvement in sleep interference[152] in PC-RCTs. There appear to be few differences between different TCAs in treatment efficacy[149]. The pain reduction occurs within 2 weeks[150]. Similar positive results have been recorded in a PC-RCTs in Canada[142], however this nortriptyline trial combined neuropathic pain conditions including PDN. Pain relief was independent of depression and there was no effect on mood by either amitriptyline[152] or nortriptyline[149]. The minimal effective dose ranged from 75–150 mg/daily[152]. Topical amitriptyline (2%) had no benefit compared to placebo[153,154].

In a single PC-RCT, fluoxetine[155], reduced the pain intensity of PHN but was less effective than desipramine. The minimal effective dose ranged from 20–60 mg/daily.

Capsaicin—PC-RCTs for PHN were identified for high dose (8%) topical capsaicin. It provided significantly greater pain relief and more long-lasting (12 weeks) than control (low dose capsaicin, 0.04%), but this difference was modest in one study[156] and not different in

another[157]. In subsequent trials, high concentration capsaicin was significantly more beneficial than the low dose control[158,159] and the first time period of significance was 2 weeks after therapy[159]. Low dose (<0.075%) topical capsaicin has been shown to be effective in the reduction of pain intensity, quality of life, and patient impression of relief[160]. The pain reduction occurs within 4 weeks after four times daily application[160].

Local Anesthetics—The lidocaine patch (5%) has been shown to be effective in the reduction of pain intensity[161–164] in PC-RCTs.

NMDA antagonists—Dextromethorphan has been shown to be ineffective in the reduction of pain intensity[165,166]. Memantine was similarly found to be ineffective[165]. Topical ketamine was ineffective in the treatment of PHN[153]. Magnesium was found to be effective in reducing PHN pain but the effect was only sustained during the intravenous infusion[167].

Mixed ARI / Opioid—Tramadol has been shown to be effective in the reduction of pain intensity and improvement in quality of life[168,169], sleep improvement[169], and social and physical function[169]. Relief onset was within 14 days[168]. The average analgesic dose was 50–200 mg/daily[169].

NSAIDs—COX-2 inhibitors were ineffective in the treatment of PHN related pain[170]. A single small trial found that topical diclofenac (1.5%) was effective in relieving neuropathic pain from CRPS and PHN, unfortunately the number of PHN patients (n=3) is insufficient to make any condition specific conclusion[171]. Ibuprofen had no benefit in a single trial[172].

Miscellaneous—Intradermal injection of Botulinum toxin A to the painful skin has been shown to be effective in the reduction of pain intensity[173,174], improvement in sleep interference[173,174], reduction in opioid use[173] for up to 12–16 weeks[173,174]. The pain reduction occurs within 1 week[173,174]. Lorazepam had no benefit compared to placebo[175].

Combination Therapy—The combination two effective medications such as nortriptyline/gabapentin[142], and morphine/gabapentin[141] has been shown to be more effective than either medication alone in the reduction of pain intensity, improvement in sleep interference, quality of life, and mood with reduction in common side effects. The lower side effects were attributable to lower dosages of the individual medications needed to achieve the same or greater pain reduction.

Painful Diabetic Neuropathy (PDN)

The World Health Organization estimates 150 million people had diabetes in the year 2000 and project 366 million by the year 2030[176]. The prevalence of peripheral neuropathy in patients with diabetes was 43%, and higher in type 2 (51%) than in type 1 (26%)[177]. The treatment of PDN includes the use of prescription medications that have FDA-approval for PDN management and those that do not (Table 6).

Membrane Stabilizers—Pregabalin (300mg/daily) has been shown to reduce ‘worst possible’ pain intensity by 1.5 points (NRS) and 1.6 (VAS) 1 week after treatment inception which remained significant during the course of an 8-week multicenter PC-RCT[178].

Furthermore, it improved mood, reduced sleep interference, and was associated with a significant impression of improvement assessed by the patient and clinician. In a separate trial, 52% of patients with baseline pain intensity in the high moderate to severe range had >50% relief compared to 24% in the placebo group over a 12 week RCT yielding a number needed to treat (NNT) of 3.6[138]. Similar positive results have been seen in PC-RCTs in China, Canada, Japan, Europe and Korea[137,179–182]. Subsequent RCTs found no improvement in pain intensity when using 150mg/daily[183], 300mg/daily[184,185] but curiously patients in the lower dose groups had a significantly impression of improvement in their global well-being as compared to placebo[183]. Earlier comparative studies showed 300mg was similarly effective to 600mg[186].

Gabapentin has been shown to be effective in the reduction of pain intensity[141,142,187] and improvements in mood[187], sleep[142,187], quality of life[141,142,187], patient and clinician[187] reported improvement in pain, and hemodialysis associated pruritus[188] in PC-RCTs. The pain reduction was found to occur within 4 weeks[142,187]. Similar results have been recorded in PC-RCTs performed in Canada[141,142], however these trials included various types of neuropathic pain conditions including PDN. The minimal effective dose ranged from 1800 – 2400 mg/daily[141,142,189,190]. The gastro-retentive gabapentin (Gr-G) formulation of gabapentin[191], but not the gabapentin pro-drug (gabapentin encarbil, Pd-G)[184] has shown similar efficacy and both show similar side effect profiles to the original formulation of gabapentin. Of note, pregabalin was included as a positive control in the enacarbil study and its results on pain intensity did not replicate earlier studies[184].

Topiramate has been shown to be borderline effective in the reduction of pain intensity, improvement in sleep interference, quality of life, and mood[192] in two PC-RCTs[192,193], but ineffective in all domains in two others[193]. In the positive trials, the pain reduction occurs within 8 weeks[192]. The most consistent finding in all trials was weight loss. Significantly more subjects lost weight in the topiramate group than placebo control subject[192]. In the positive trials, the minimal effective dose ranged from 100 mg/daily[192,193].

Lamotrigine has been shown to be minimally effective in the reduction of pain intensity in two PC-RCTs[194,195] and no change in one[195]. Subjects had no improvement in sleep interference, quality of life, patient reported improvement in pain, or mood and the most common side effect was rash[194,195]. In the positive trials, the minimal effective dose ranged from 400 mg/daily and pain reduction occurs within 6 weeks.

Oxcarbazepine has been shown to be borderline effective in the reduction of pain intensity[196] in a single PC-RCT, but no different in two PC-RCTs[197,198]. The pain reduction occurs within 2 weeks[196]. The minimal effective dose in the single positive study was 1800 mg/daily[196].

In a small PC-RCT, zonisamide statistically improved pain intensity over placebo, however this did not meet the authors pre-prescribed criteria for significant reduction of 2 points in pain intensity score[199].

ARIs—Duloxetine has been shown to be effective in the reduction of pain intensity[200,201], improvement in sleep interference due to pain[200,201], quality of life[200,201], patient[200] and clinician[200] reported improvement in pain and mood[200] in PC-RCTs. The pain reduction occurs within 1 week[200,201]. Similar results have been shown in multicenter PC-RCTs[202–204], but a single Chinese PC-RCT did not replicate the pain relief[205]. Pain relief was found to be dose dependent and the minimal effective dose was 60 mg/daily[200,202]. No difference was noted between 60mg and 120mg/daily[201]. Longer-term studies showed maintenance of pain relief to 6 months[206] and 1 year[207].

Venlafaxine has been shown to be effective in the reduction of pain intensity, patient and clinician reported improvement in pain in PC-RCTs[208]. The pain reduction occurs within 2[209] or 6[208] weeks and the NNT was 4.5[208]. Similar efficacy results have been reported in another small PC-RCTs[209]. The minimal effective dose ranged from 150–225 mg/daily[208].

The TCAs desipramine[210,211], imipramine[212] and amitriptyline[210,213–215], have demonstrated effectiveness in the reduction of pain intensity and improvement in sleep interference[212,214,215] in PC-RCTs. No PC-RCTs were identified for nortriptyline. The pain reduction occurs within 3–5 weeks[210–213]. Pain returned within 2 weeks of TCA discontinuation[211]. Pain relief was independent of depression and there was no effect on mood by either amitriptyline or desipramine[210,213] except in a single desipramine trial[211]. The minimal effective dose ranged from 90–150 mg/daily[212,213] and the effects of amitriptyline were dose dependent to 150mg/daily[213].

Paroxetine[216], but not fluoxetine[210], reduce the pain intensity of DPN, improvement in sleep interference and improve nighttime pain. The pain reduction occurs within 1–5 days[216]. Similar efficacy results have been reported in another small PC-RCT[209]. The minimal effective dose ranged from 40–50 mg/daily[217].

Capsaicin—Low dose (<0.075%) topical capsaicin has been shown to be effective in the reduction of pain intensity[218,219], improvement in sleep interference[219], quality of life[218], and clinician impression of relief[218,220]. The pain reduction occurs within 8 weeks after four times daily application[218]. Ultra-low dose (0.025%) topical capsaicin provided no better pain relief than placebo[221]. No PC-RCTs for PDN were identified for high dose (8%) topical capsaicin.

Local Anesthetics—Oral mexiletine has been shown to be effective in the reduction of pain intensity in 1 trial[222], but no different from placebo in 2 trials[223,224]; however each trial suffered from small size. One trial noted improvement in sleep interference and nocturnal pain at high doses (675mg/daily)[225] with side effects including stomach pain, diarrhea, and nausea.

NMDA antagonists—Dextromethorphan has been shown to be effective in the reduction of pain intensity[165,166]. The pain reduction occurs within 4 weeks[166]. In both trials, high dose dextromethorphan was used. The minimal effective dose ranged from 250 to 450 mg/daily[165,166]. Two PC-RCTs of topical ketamine for DPN found no pain intensity reduction[153,226]

Mixed ARI / Opioid—Tapentadol has been shown to be effective in the reduction of pain intensity[227,228], Vinik et al[227] reported improvement in pain in PC-RCTs. The pain reduction occurs within 2–3 weeks[227]. The minimal effective dose ranged from 100 mg/daily[227,228]. Tramadol has been shown to be effective in the reduction of pain intensity and improvement in social and physical functioning in a single PC-RCT[229]. The average analgesic dose was 210mg/daily.

Miscellaneous—Intradermal injection of BoNT-A to the painful foot has been shown to be effective in the reduction of pain intensity[230], pain sensory threshold[231], improvement in sleep interference[230], quality of life[230]. The pain reduction occurs within 1 week[231]. Inhaled cannabis reduced spontaneous pain associated PDN for a short duration in a dose-dependent fashion but had significant negative cognitive effects[232]. Nabilone was significantly better than placebo at reducing pain intensity and improving sleep quality[233]. Topical clonidine (0.1%) with a daily dose of 3.9 mg applied to the painful feet produce significant reduction in pain compared to placebo. In patients with intact peripheral nociceptor function, the response to topical clonidine was significantly greater[234].

Combination Therapy—The combination of two effective medications such as nortriptyline/gabapentin[142], and morphine/gabapentin[141] has been shown to be more effective than either medication alone in the reduction of pain intensity, improvement in sleep interference, quality of life, and mood with reduction in common side effects. The lower side effects were attributable to lower dosages of the individual medications need to achieve the same or greater pain reduction.

Radicular Pain (RP)

Characterized by radiating pain in one or more dermatomes that may be accompanied by other nerve root irritation symptoms and/or decreased function, the estimated lifetime prevalence estimates is 1.2% to 43%[235]. In 60% of patients with acute RP (<12 weeks of symptoms), it completely or partially resolves. Unfortunately, about 32% of the patients have pain after 1 year[236]. Although this is one of the most common neuropathic pain conditions, most commonly used neuropathic pain medications have either no efficacy or limited efficacy when studied in rigorous RCTs (Table 7).

Membrane Stabilizers—Two PC-RCTs examining the pain reduction efficacy of pregabalin for chronic radicular pain did not find any benefit as compared to placebo[237,238]. Similarly, there was no improvement in quality of life or patient reported improvement in pain. A trial that alludes to being RCT (methods section lacks sufficient detail to definitively determine) and suffers from trial design flaws reported a modest benefit of pregabalin for L5 radicular pain but not for lower nerve root distribution radicular pain[239].

Gabapentin has been shown to be effective in the reduction of pain intensity and improvement in walking distance in a single PC-RCT[240] but no pain relief was found in a subsequent larger trial[29].

Topiramate has been shown to be ineffective in the reduction of pain intensity[241].

ARIs—Duloxetine has been shown to be effective in the reduction of pain intensity and quality of life in a single PC-RCT[22]. The pain reduction occurs within 3 weeks. In a small trial, milnacipran was found to produce a significant decrease in radicular pain compared to placebo, but no secondary outcome such as quality of life, mood or physical function were improved[242].

Amitriptyline, at 25mg/daily[243], was shown to be modestly effective in the reduction of pain intensity and had common side effects in a single PC-RCT. Nortriptyline was found to be effective in pain reduction, but not mood or quality of life in a single trial[18], but had no effect in a subsequent trial[244]. Interestingly, in the second trial the active comparator, morphine, was also ineffective and produced no greater pain relief than the inert placebo[244].

NSAIDs—Indomethacin was found to be effective in the reduction of chronic radicular pain in a PC-RCT[245], but not others[246].

Complex regional pain syndrome (CRPS)

Complex regional pain syndrome (CRPS) has had different names over the years and with different criteria for diagnosis. The older criteria were proposed by Kozin et al in 1981[247], Veldman et al in 1993[248], and van de Beek et al in 2002[249], none of which were subjected to rigorous testing of its psychometric properties. To be more definitive and consistent in the diagnosis of CRPS, the International Association for the Study of Pain (IASP) and the Budapest Criteria were proposed. The IASP criteria[250] has a good sensitivity but with low specificity[251] while the Budapest Criteria appears to have better characteristics[252]. A validation study noted the IASP criteria to have a high diagnostic sensitivity but low specificity[253], resulting in a relatively high rate of false positive diagnoses and unnecessary treatments. The Budapest criteria, on the other hand showed the same high sensitivity but with improved specificity[253] and is therefore recommended in both clinical and research settings[254]. There are two types of Budapest criteria, a clinical and a research diagnostic criteria.

Only papers that used the Budapest or IASP criteria to diagnose CRPS were included except two articles on biphosphonates that used the Kozin criteria. These two studies were discussed because bisphosphonates are an emerging treatment of CRPS. The PC-RCTs on calcitonin also did not employ the IASP or Budapest criteria but were discussed since clinicians need to know the results as some patients inquire about the drug. Exclusion criteria included papers that used the older criteria[248,249] other than the one by Kozin[247] and studies on intravenous regional or neuraxial treatments.

Ketamine—A study showed IV ketamine to have significantly better pain relief when compared to placebo[255] (Table 8). In this study, ketamine was administered over a 4-day period. The dose was given in an individualized stepwise fashion, started at 1.2 mcg kg^{-1} min (approximately 5 mg/h for a 70 kg patient) to a maximum of 7.2 mcg kg^{-1} min (30 mg/h in a 70 kg patient). Ketamine was noted to be significantly better in terms of pain relief. However, the difference was gone at 12 weeks and there was no difference between the treatment groups in their secondary outcomes. Another study showed superiority of

ketamine infusion over placebo[256] in relieving pain, reducing allodynia, thermal and deep pressure pain thresholds, and improving motor function (Table 8).

A PC-RCT showed 10% topical ketamine to be effective in relieving the allodynia of patients with CRPS[257] (Table 8). The plasma levels of ketamine were undetectable, ruling out any systemic effect of the drug. Interestingly, 17 of the 20 patients met the Budapest criteria while all 20 patients met the IASP criteria.

Bisphosphonates—Oral alendronate, 40 mg every day for 8 weeks, was compared with placebo[258]. Alendronate was noted to be superior to placebo in terms of decrease in pain and edema, tolerance to pressure, and joint mobility (Table 9). Alendronate when compared to placebo via the intravenous route was also noted to be significantly better than placebo[259].

A single intravenous infusion of 60 mg pamidronate resulted in improvements in pain scores, patient's global assessment of disease score, and functional assessment (Table 8)[260]. Intravenous clodronate, 300 mg, given daily for 10 consecutive days was noted to have better results (pain scores, clinical global assessment) over placebo[261]. Neridronate was also noted to be significantly better than placebo in a multicenter trial[262]. The dose was 100 mg neridronate given four times over days; improvements were noted with regards to pain on passive motion, McGill Pain Questionnaire and SF-36. None of the patients had CRPS at one year follow-up.

Intravenous immunoglobulin—The possibility that immune mechanisms are involved in the pathogenesis of CRPS led investigators to examine the effect of intravenous immune immunoglobulin (IVIG) on this syndrome. An initial open-label study revealed the efficacy of IVIG in relieving the pain from different chronic pain syndromes, including CRPS[263]. Their findings led the authors to proceed to a PC-RCT[264] (Table 8). Twelve patients who had CRPS for 6 to 30 months refractory to standard treatment and had pain intensities greater than 4 on an 11-point rating scale were randomized to either IVIG (0.25 g.kg per day, total dose of 0.5 g/kg) or placebo. The intervention was given for two consecutive days, the crossover infusion was given 28 days after the initial infusion. Pain diaries were made by the patients daily until 28 days after the last infusion, follow-up was also made 8 weeks later. The IVIG treatment was significantly better than placebo ($P < 0.001$), the average pain intensity was 1.6 less after the IVIG treatment and no adverse effects were noted.

Intravenous magnesium—Two studies examined the effect of IV magnesium on CRPS[265,266]. One study involved 10 patients, 8 received the IV magnesium while 2 were given saline[265]. The patients who had the magnesium infusion had pain relief and improvements in their impairment level and quality of life. Although randomized and double-blinded, the results of the two patients who had saline were not presented or analyzed and the results between the two treatments were not compared. The same group of investigators later performed a PC-RCT[266]. Fifty nine patients with CRPS type I criteria were randomized into either IV magnesium (29) or placebo (27)[266]. The magnesium dose was 70 mg/kg for 4 hours a day for 5 consecutive days. Outcome measures included pain relief, impairment score, functional limitation, and quality of life. There was no significant difference between magnesium and placebo in terms of pain relief and impairment score at

different time points during the trial. The authors' conclusion was that magnesium provided insufficient benefit over placebo in patients with CRPS type 1[266].

Intravenous mannitol and intravenous parecoxib—A study compared mannitol, an oxygen radical scavenger with placebo[267]. The investigators noted that 10% mannitol in one liter, given over 4 hours for 5 consecutive days, was not significantly better than placebo in terms of pain relief or any of the outcome measures. A PC-RCT study compared IV parecoxib, 20 mg twice daily for two consecutive days, with saline[268] using low pressure pain threshold as the primary criteria. The study was stopped after 20 patients because of authors' difficulty in their recruitment and the absence of improvement in the parecoxib group in any of their primary and secondary outcomes.

Oral steroids—Three studies showed superiority of oral steroid over placebo[269,270] or piroxicam[271]. However, the studies were hampered by the use of physical and radiological findings to diagnose CRPS[269,271] or use of the Kozin's criteria[270]. A recent open-label study using the Budapest criteria showed that oral prednisolone did not reduce the average pain intensity in patients with CRPS of greater than 3 months duration[272]. To date, there is no PC-RCT on oral steroids in CRPS patients diagnosed by the IASP or Budapest criteria.

Membrane Stabilizers—A crossover study compared gabapentin with placebo[273] (Table 9). The dose of gabapentin was started at 600 mg daily then titrated to 600 mg TID, treatment was for three weeks followed by a two week washout before the crossover portion of the study of another three weeks of treatment. There was significantly better pain relief with gabapentin during the first phase, less during the second treatment phase, and the combined phases did not show significant result. Global perceived pain relief showed significant more treatment effect that was more pronounced in the first treatment period. Although sensory deficits were significantly reversed with gabapentin, there was no difference between gabapentin and placebo in the other outcome measures. Interestingly, there was an unexplained increase of pain during the washout period that may have lessened the treatment effect in the second phase of the study. In the clinical setting, most patients are treated for at least several months as long as there is pain relief so we do not know the effect of long-term treatment with gabapentin based on this study.

Another study showed the superiority of gabapentin over placebo in patients with neuropathic pain syndrome, including CRPS[274]. Although diagnosis was based on the IASP criteria, the study looked at other neuropathic pain syndromes and the results in the patients who had CRPS were not shown separately. Furthermore, patients who previously did not respond to gabapentin were not enrolled in the study.

Memantine—A prospective open series showed reduction of pain in patients with CRPS[275]. This led investigators to compare morphine (30 mg daily) with or without memantine (40 mg daily) in a PC-RCT[276]. The authors showed that only the combination reduced the pain and disability. Unfortunately, the authors used the van de Beek criteria to diagnose CRPS.

Tadalafil—Tadalafil inhibits phosphodiesterase-5 (PDE-5), relaxes smooth muscle and causes vasodilatation reversing decreased regional blood flow in CRPS. A PC-RCT showed a non-statistically different temperature change[277]. However, there was a statistically and clinically significant reduction in pain with tadalafil at the end of the study (Table 9). The tadalafil dose was 10 mg daily for 4 weeks then 20 mg for another 8 weeks.

Calcitonin—None of the controlled studies on calcitonin employed the psychometrically-validated Budapest or IASP criteria[278–282]. Two PC-RCT studies on nasal calcitonin showed conflicting results, one noted superiority of calcitonin[278] while the other did not[279]. One study used the Kozin criteria[247] while the other based their diagnosis only on the presence of swelling and stiffness after a Colles fracture[279]. Another randomized study on nasal calcitonin that was single-blinded and based their diagnosis on clinical symptoms and physical exam findings; the authors noted no difference between nasal calcitonin to paracetamol[281]. Two studies on parenteral calcitonin are not discussed because one study was not blinded[280] while randomization or blinding was not discussed in the other study[282]. In summary, one randomized trial showed superiority of calcitonin over placebo[278] while two randomized trials showed improvements but no superiority over placebo[279] or paracetamol[281]. Since the studies on calcitonin did not employ the Budapest or IASP criteria and the diagnosis of CRPS could not be assured in these studies, we cannot determine the real efficacy of calcitonin in this syndrome.

Topical treatments: DMSO—Dimethylsulfoxide (DMSO) is a free radical scavenger, the rationale for its use is the premise that CRPS is induced by an inflammatory response to tissue injury mediated by overproduction of toxic oxygen radicals. A PC-RCT study showed DMSO 50% in fatty cream, given for two months, was significantly better than placebo in patients with acute reflex sympathetic dystrophy (RSD)[283]. Improvements were noted in RSD scores and pain relief at two-month follow-up. Another study was a randomized, double-dummy controlled trial that compared DMSO with N-acetylcysteine (NAC) another free radical scavenger[284]. The investigators showed improvements but with equal efficacy between the two drugs. Unfortunately, both studies diagnosed RSD with the 1993 Veldman criteria.

BoNT-A—The efficacy of subcutaneous BoNT-A in relieving allodynia from chronic neuropathic pain led investigators to perform a PC-RCT on subcutaneous BoNT-A in patients with CRPS[285]. BoNT-A was injected at a dose of 5 units per site, half of the dose was injected intradermally while half was injected subcutaneously. The sites ranged from 10 to 40 sites with a total dose of 40–200 units. The outcome measures included several questionnaires and quantitative sensory testing. The study had to be stopped after an interim evaluation showed no relief at 3 or 8 weeks after treatment and 8 of 9 patients considered the treatment to be intolerable and stated that they would not consider the injections as treatment for their pain[285].

TNF-alpha inhibitors—A study noted the lack of superiority of infliximab, 5 mg/kg given at week 0, 2 and 6 over placebo in terms of total impairment level sum score (redness,

swelling, increased temperature, pain dysfunction), inflammatory mediators in the blister fluid, and other outcome measures (Table 8)[286].

Conclusions

The scope of this review on non-opioid pharmacotherapy was broad and all-encompassing for the most common chronic pain syndromes that current pain management physicians treat. A large body of knowledge exists, ranging from case reports to meta-analyses. Considering 2468 articles were screened and strict inclusion criteria were employed, the paucity of high quality prospective, blinded, RCTs investigating the pharmacologic therapies that are so commonplace in our field was disappointing (Supplemental Table 1). The effect sizes for many treatments were small, including some of those that are FDA-approved. IMMPACT guidelines have reported on the changes in pain scores that are consistent with a "significant" improvement in pain – a change of 30% in numerical pain rating or more. Many of the studies presented here do not provide this level of reduction, yet have shown statistical significance. Mainstays of treatment - such as NSAIDs, membrane stabilizers, muscle relaxants, and amine reuptake inhibitors – seemed to have positive findings for a few conditions, however, the robustness of pain reduction were modest at best.

The following paragraphs will summarize the findings of positive blinded, controlled, randomized clinical studies on non-opioid medications for chronic pain conditions. For chronic low back pain, non-opioid medications that have been shown to provide significant pain reduction include: NSAIDs (naproxen, etoricoxib, valdecoxib, rofecoxib, celecoxib, diclofenac, piroxicam, and indomethacin), ARIs (doxepin, desipramine, nortriptyline, duloxetine, and maprotiline), membrane stabilizers (topiramate), muscle relaxants (only short-term relief for carisoprodol, cyclobenzaprine, and diazepam), mixed ARI/opioid (tramadol, tramadol/acetaminophen, and tapentadol), topical capsaicin cream, botulinum toxin type A, and tanezumab.

For patients with myofascial pain syndrome, the following medications have been shown to be efficacious in reducing pain levels: NSAIDs (diclofenac trigger point injections and topical diclofenac sodium patch), muscle relaxants (methocarbamol), topical lidocaine patch, bupivacaine trigger point injections, and botulinum toxin type A. Fibromyalgia has been well-studied and the following non-opioids have been shown to reduce pain scores significantly: ARIs (milnacipran, duloxetine, amitriptyline, fluoxetine, controlled-release paroxetine), membrane stabilizers (pregabalin and gabapentin), muscle relaxants (cyclobenzaprine), mixed ARI/opioid (tramadol/acetaminophen), NMDA antagonists (memantine), opioid antagonists (low-dose naltrexone), and cannabinoids (nabilone).

For the neuropathic pain condition post-herpetic neuralgia, significant positive findings with regards to pain reduction were shown in: membrane stabilizers (pregabalin, gabapentin, and levetiracetam), ARIs (nortriptyline, desipramine, amitriptyline, and fluoxetine), topical capsaicin, lidocaine patch, mixed ARI/opioid (tramadol), and botulinum toxin type A. In painful diabetic neuropathy, the following non-opioid medications have proven beneficial to improve pain scores: membrane stabilizers (pregabalin, gabapentin, topiramate, lamotrigine, oxcarbazepine, and zonisamide), ARIs (duloxetine, venlafaxine, desipramine, imipramine,

amitriptyline, and paroxetine), topical capsaicin, local anesthetics (mexiletine), NMDA antagonists (dextromethorphan), mixed ARI/opioid (tapentadol extended-release and tramadol), botulinum toxin type A, cannabinoids (inhaled cannabis and nabilone), and topical clonidine. Non-opioid medications found to be effective for pain relief in radicular pain are: ARIs (duloxetine, amitriptyline, and nortriptyline) and NSAIDs (indomethacin). Finally, for complex regional pain syndrome, the medications reported to reduce pain score intensity include: IV ketamine, bisphosphonates (oral alendronate, IV pamidronate, IV clodronate, and neridronate), IVIG, gabapentin, and DMSO. We cannot make concluding statements on calcitonin based on the published studies.

Our review has its limitations. Reviewing and including all of the primary literature per pain condition was simply not feasible within the scope of this review due to the large number of medications included. Furthermore, chronic pain specialists see pain conditions outside of the included syndromes (e.g., chronic abdominal pain, entrapment neuropathies, chronic pelvic pain, painful bladder syndrome) and due to space limitations; we were not able to be fully inclusive of all non-malignant chronic pain syndromes. Instead, we chose to include the most common non-cancer pain syndromes seen in most pain management clinics. A large majority of articles were reviewed that had evidence for many pharmacologic agents, however, we only included the higher-quality level evidence of blinded RCTs. We excluded non-English language articles and did not search for abstract only publications. Due to the narrative nature of this review, reporting of bias was not included or performed.

The evidence base has its limitations as well, which may potentially affect the quality of the included studies. Our inclusion criteria were designed to include only the higher-quality levels of evidence that are inherent in blinded RCTs. However, given our narrative review methodology did not incorporate assessments or grading of the quality and/or bias of the included individual studies, there does exist a possibility that other aspects of research methodology that affect bias and quality in a negative way could be present in our included studies and thus, this is a limitation of the present review. Populations studied likely had heterogeneity even within a specific pain condition population. Moreover, assessment of “pain outcomes” varies from study to study, which makes it difficult to compare one study to the next, even within a specific pain condition population. Furthermore, many studies were funded by industry, for example, the manufacturer funded the majority of placebo-controlled trials of duloxetine for chronic low back pain and nearly all trials of tramadol and tapentadol.

Even with its substantial societal impact, we have not seen the type of developments in the treatment of the chronic pain that have been garnered in other fields of medicine. There are explanations and challenges in performing transformative pain research that can explain this limited progress. First, pain research is tragically underfunded in both the private and public sectors. This is distressing on multiple levels and likely distracts talented individuals from pursuing an academic or industry pain research career. Furthermore, although efforts are ongoing to try and improve and prioritize federal funding for pain research, these incremental actions may prove to be insufficient for the enormity of the public health problem. Secondly, despite chronic pain being the most prevalent public health condition in the United States, the magnitude of the problem is not well-recognized by the general

public, as indicated by a recent poll of U.S. adults where only 18% of respondents identified chronic pain as a major public health problem[287]. Some recommended changes to improve chronic pain research include an attitude/culture shift, a refocusing and refinement of research approaches and methodology, improved pain research education, and a major investment by the public and private funding sectors[288].

More research is needed to determine effective and mechanisms-based treatments for the chronic pain syndromes discussed in this review. Studies where a long-term follow up are provided would be beneficial in a placebo-controlled, double-blind fashion, however, the ethical implications of long-term placebo use are understood. More research on combinations of pharmacotherapeutics are needed to determine whether incremental or synergistic benefits are seen and whether or not these are sequence-reliant. Maintaining rigorous methodology where the same outcome measures following IMMPACT recommended guidelines (pain outcome measures, quality of life measures, functioning measures) would likely allow for better consistency and reproducibility, which is of utmost importance in guiding evidence-based care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Included Chronic Pain Conditions and Non-Opioid Drug Classes

Chronic Pain Condition	Non-Opioid Drug Class
Chronic Low Back Pain	Acetaminophen
Myofascial Pain Syndrome	NSAIDs
Fibromyalgia	Amine Reuptake Inhibitors
Post-Herpetic Neuralgia	Membrane Stabilizers
Painful Diabetic Neuropathy	Muscle Relaxants
Radicular Pain	Mixed Amine Reuptake Inhibitor/Opioid
Complex Regional Pain Syndrome (CRPS)	Topical Therapies Botulinum Toxins NMDA antagonists Opioid Antagonists (Low-Dose Naltrexone) Local Anesthetics Steroids Cannabinoids or Cannabis Miscellaneous Specific to CRPS: Biphosphonates, calcitonin, IV immunoglobulin, IV magnesium, IV mannitol, tadalafil, TNF alpha inhibitors

NSAIDs: Non-steroidal anti-inflammatory drugs; NMDA: N-methyl-D-Aspartate

Table 2

Chronic Low Back Pain – Effective Medications based on Included Studies

Chronic Low Back Pain – Effective Medications	
FDA On-Label	**Off-Label**
Acetaminophen	
None	None
NSAIDs	
None	Naproxen, Etoricoxib, Valdecoxib, Rofecoxib, Celecoxib, Diclofenac, Piroxicam, Indomethacin
ARIs	
None	Desipramine, Doxepin, Nortriptyline, Duloxetine, Maprotiline
Membrane Stabilizers	
None	Topiramate
Muscle Relaxants	
None	Carisoprodol, Cyclobenzaprine, Diazepam
ARI/Opioid	
None	Tramadol, Tramadol/acetaminophen, Tapentadol
Topical Capsaicin	
None	Capsaicin cream
Local Anesthetics	
None	None
NMDA Antagonists	
None	None
Miscellaneous	
None	Botulinum Toxin Type A, Tanezumab

FDA: Food and Drug Administration; NSAIDs: non-steroidal anti-inflammatory drugs; ARI: amine reuptake inhibitor; NMDA: N-methyl-D-aspartate

Table 3

Myofascial Pain Syndrome – Effective Medications based on Included Studies

Myofascial Pain Syndrome – Effective Medications	
FDA On-Label	**Off-Label**
NSAIDs	
None	IM Diclofenac (short-term relief), Topical Diclofenac Sodium patch
ARIs	
None	None
Membrane Stabilizers	
None	None
Muscle Relaxants	
None	Methocarbamol
ARI/Opioid	
None	None
Topical Capsaicin	
None	None
Local Anesthetics	
None	Topical Lidocaine Patch, 0.5% Bupivacaine IM injection
NMDA Antagonists	
None	None
Miscellaneous	
None	Botulinum Toxin Type A

FDA: Food and Drug Administration; NSAIDs: non-steroidal anti-inflammatory drugs; ARI: amine reuptake inhibitor; NMDA: N-methyl-D-aspartate

Table 4

Fibromyalgia – Effective Medications based on Included Studies

Fibromyalgia – Effective Medications	
FDA On-Label	**Off-Label**
NSAIDs	
None	None
Amine Reuptake Inhibitors (ARI)	
Duloxetine, Milnacipran	Amitriptyline, Fluoxetine,Paroxetine (controlled-release)
Membrane Stabilizer	
Pregabalin	Gabapentin
Muscle Relaxants	
None	Cyclobenzaprine
ARI/Opioid	
None	Tramadol/acetaminophen
Opioid Antagonists	
None	Low-dose Naltrexone
NMDA Antagonists	
None	Memantine
Local Anesthetics	
None	None
Miscellaneous	
None	Nabilone

FDA: Food and Drug Administration; NSAIDs: non-steroidal anti-inflammatory drugs; ARI: amine reuptake inhibitor; NMDA: N-methyl-D-aspartate

Table 5

Post-herpetic Neuralgia – Effective Medications based on Included Studies

Post-herpetic Neuralgia – Effective Medications	
FDA On-Label	**Off-Label**
Topical (non-local anesthetic)	
Capsaicin 0.025%; 0.075%; 0.025%–10%–25%; 0.035%; 0.1%; 8%; 0.25%; Capsaicin Patch (8%)	None
Amine Reuptake Inhibitors (ARI)	
None	Amitriptyline, Desipramine, NortriptylineFluoxetine
Membrane Stabilizers	
Gabapentin, Gabapentin GR, Gabapentin Enacarbil, Pregabalin	Levetiracetam
ARI/Opioid	
None	Tramadol
Local Anesthetics	
Lidocaine Patch (5%)	None
NMDA Antagonists	
None	None
Miscellaneous	
None	Botulinum Toxin Type A

FDA: Food and Drug Administration; ARI: amine reuptake inhibitor; NMDA: N-methyl-D-aspartate

Table 6

Painful Diabetic Neuropathy – Effective Medications based on Included Studies

Painful Diabetic Neuropathy – Effective Medications	
FDA On-Label	**Off-Label**
Topical (non-local anesthetic)	
Capsaicin 0.025%; 0.075%; 0.025%–10%–25%; 0.035%; 0.1%; 8%; 0.25%	Clonidine
Amine Reuptake Inhibitors (ARI)	
Duloxetine	Desipramine, Imipramine, Amitriptyline,Venlafaxine, Paroxetine
Membrane Stabilizers	
Pregabalin	Gabapentin, Topiramate, Lamotrigine, Oxcarbazepine, Zonisamide
ARI/Opioid	
Tapentadol ER	Tramadol
Local Anesthetics	
None	Mexiletine
NMDA Antagonists	
None	Dextromethorphan
Miscellaneous	
None	Intradermal Botulinum Toxin Type A,Cannabis, Nabilone

FDA: Food and Drug Administration; ARI: amine reuptake inhibitor; ER: extended release; NMDA: N-methyl-D-aspartate

Table 7

Radicular Pain – Effective Medications based on Included Studies

Radicular Pain – Effective Medications	
FDA On-Label	**Off-Label**
Topical (non-local anesthetic)	
None	None
Amine Reuptake Inhibitors (ARI)	
None	Duloxetine, Milnacipran, Amitrptyline
Membrane Stabilizers	
None	None
ARI/Opioid	
None	None
Local Anesthetics	
None	None
NMDA Antagonists	
None	None
Miscellaneous	
None	Indomethacin

FDA: Food and Drug Administration; ARI: amine reuptake inhibitor; NMDA: N-methyl-D-aspartate

Table 8

Randomized Controlled trials on Efficacious Intravenous Drugs for Complex Regional Pain Syndrome

Study: CRPS Type I Criteria	Treatment	Results	Comments	Adverse Effects
Sigtermans et al; IASP criteria; P, R, DB	Ketamine, 4.2 day infusion, stepwise tailored dose, median (range dose) of 22 +/−2 mg/h/70 kg; 60 patients, 30 per group	Significantly better results with ketamine in terms of pain relief, no difference in secondary outcomes	Differences in pain relief maintained up to 11 weeks, gone at 12w	Nausea, vomiting, psychomimetic effects (drug high, hallucinations)
Scharztman et al; IASP criteria; P, R, DB, PC;	Ketamine infusion for 4h x 10d; 0.35 mg/kg/h not to exceed 25 mg/h (100 mg over 4h); 19 subjects, 9 had ketamine	Significantly better results with ketamine over placebo in many pain parameters	Study terminated early as interim analysis showed no improvement with placebo in any of the parameters. Also, additional experience showed 50 mg/h (200 mg over 4h) gave greater and longer relief	Nausea, tiredness, dysphoria, headache (midazolam and clonidine given during infusion)
Adami et al; Kozin criteria; P, R, DB	Alendronate, 7.6 mg in 250 mL saline vs saline infusion daily x 3d followed by an open-label treatment; 20 patients, 10 per group	Improvement in pain, tenderness, swelling were significantly better with alendronate	Patients in the placebo group later responded in the open-label study	Fever
Robinson et al; IASP criteria; P, R, DB	Pamidronate 60 mg as a single infusion vs placebo; 27 patients, 14 had pamidronate	Pain scores, global assessment, physical function (SF-36) were better in the pamidronate group	There was variability of response to pamidronate among the patients	Influenza-like symptoms, infusion site symptoms (erythema, discomfort)
Varenna et al; Kozin criteria; P, R, C, DB	Clodronate 300 mg daily x 10 consecutive days vs placebo; 32 patients, 15 had clodronate	Significantly better results in the clodronate group	Significantly better improvements in the placebo group when treated openly with clodronate	Polyarthralgia, fever
Varenna et al; Budapest criteria; P, R, C, DB	Neridronate, 100 mg given four times over 10 days vs placebo; 82 patients, 41 per group	Significantly better results (evoked pain, McGill pain Questionnaire, SF-36)	Better response in the placebo group during the open-label phase.	Duration less than 2 days: Fever, chills sweating, postural hypotension, nausea, vomiting, diarrhea, lethargy, anxiety, restlessness, sleep disturbance, headache. S/s of anaphylactoid reaction (nasal congestion, itch, wheeze, exanthema) none needing treatment.
Goebel et al; Budapest criteria; P, R, DB, C	IVIG, total dose of 0.5 g/kg (0.25 g.kg/day) vs placebo; 12 patients, 7 of 7 patients assigned to IVIG finished both phases while 5 of 6 patients initially given saline completed the crossover portion of the study	Significantly better results with IVIG in terms of pain scores, limb symptoms scale		None
Dirckx et al, IASP criteria, P, R, DB, PC	Infliximab, 5 mg/kg given at 0, 2, 6 weeks; 13 patients (6 had infliximab)	No significant difference between the 2 groups: McGill Pain Questionnaire, cytokine levels in blister fluid	Study terminated early since results attained statistical power	Headache, hypertension, dizziness, diplopia, nausea, malaise, flu-like symptoms

C: Crossover; DB: Double-blind; IASP: International Association for the Study of Pain; IVIG: Intravenous immunoglobulin; P: Prospective; R: Randomized

Table 9

Randomized Controlled trials on the Effective Orally Administered Drugs for Complex Regional Pain Syndrome

Study: CRPS Type I Criteria	Treatment	Results	Comment	Adverse Effects
Manicourt et al, Budapest criteria; P, R, PC, DB, C	Alendronate, 40 mg orally daily x 8w vs placebo; 40 patients, 20 per group	Alendronate significantly better	Patients who continued to the open-label phase had new or dramatic improvement	Upper gastrointestinal intolerance
Van de Vusse et al; IASP criteria; P, R, DB, PC, C	Gabapentin x 3w, titrated to 600 mg TID vs placebo, 2w washout, then 3w of crossover treatment; 58 patients, 29 per group	Significantly better pain relief with gabapentin during treatment, less in second period (washout), no significant effect when both periods were combined	Sensory deficit significantly reversed with gabapentin.	Dizziness, somnolence, lethargy
Groeneweg et al, Budapest criteria; P, R, PC	Tadalafil, 10 mg for 4w then 20 mg for another 84 vs placebo; 24 patients, 12 per group	Non-statistically significant change in temperature; statistically and clinically relevant decrease in pain with tadalafil	No difference in muscle strength between groups; interventions did not improve activity levels.	None

C: Crossover; DB: Double-blind; IASP: International Association for the Study of Pain; P: Prospective; R: Randomized