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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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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 use nonopioid 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 nonmalignant 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 nonopioid analgesics for the most common noncancer 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 nonopioid 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 are not considered to be clinically significant despite statistical significance. More research is needed to determine effective and mechanism-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. (*Anesth Analg* 2017;125:1682–703)

It is estimated that more than 100 million Americans spend each day in chronic pain, at a yearly cost of more than \$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 nonopioid medications to treat chronic pain; however,

for some patients, opioid analgesics are utilized for the symptomatic treatment of chronic pain.

In 2016, in response to the increasing rates of opioid prescribing coupled with an epidemic of opioid use disorders in the United States, the Centers for Disease Control (CDC) published guidelines on the use of opioid analgesics for chronic nonmalignant pain.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 nonpharmacologic and nonopioid pharmacologic therapy is preferred for chronic pain and should be tried first.² Nonopioid pharmacotherapy includes, but is not limited to, acetaminophen, nonsteroidal 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 in which nonopioid 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),

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myofascial pain syndrome (MPS), fibromyalgia (FM), postherpetic neuralgia (PHN), painful diabetic neuropathy (PDN), radicular pain (RP), and complex regional pain syndrome (CRPS) (Table 1). These conditions were chosen for this review because they represent the most common chronic pain syndromes that current pain management physicians treat. Studies must have investigated the efficacy of nonopioid 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 article. Studies were included if their primary outcomes were the impact of the nonopioid 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 2017 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 nonopioid medication investigated was employed. The search strategy and terms are provided in Supplemental Digital Content 1, Appendix 1, <http://links.lww.com/AA/B956>. 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.

Table 1. Chronic Pain Conditions and Nonopioid Drug Classes

Chronic Pain Condition	Nonopioid Drug Class
Chronic low back pain	Acetaminophen
Myofascial pain syndrome	NSAIDs
Fibromyalgia	Amine reuptake inhibitors
Postherpetic neuralgia	Membrane stabilizers
Painful diabetic neuropathy	Muscle relaxants
Radicular pain	Mixed amine reuptake inhibitor/opioid
CRPS	Topical therapies
	Botulinum toxins
	NMDA antagonists
	Opioid antagonists (low-dose naltrexone)
	Local anesthetics
	Steroids
	Cannabinoids or cannabis
	Miscellaneous
	Specific to CRPS: bisphosphonates, calcitonin, IV immunoglobulin, IV magnesium, IV mannitol, tadalafil, TNF- α inhibitors

Abbreviations: CRPS, complex regional pain syndrome; IV, intravenous; NMDA, N-methyl-D-aspartate; NSAIDs, nonsteroidal anti-inflammatory drugs; TNF, tumor necrosis factor.

Study Selection and 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 that were recorded on the standardized extraction form.

Results

The literature searches revealed a total of 9566 citations, of which 7098 citations were excluded due to being unrelated or duplicates; 2468 citations were screened, and 2197 were excluded for the following reasons: review articles (narrative or systematic); meta-analyses; case reports/series; observational studies; retrospective studies; nonrandomized studies; nonblinded studies; acute pain population; nonpain efficacy primary outcome; publication a protocol for an upcoming trial; and studies that did not have a control arm (either placebo or active comparator). The final number of studies included that investigated the efficacy of nonopioid analgesics on chronic pain syndromes was 271 (Supplemental Digital Content 2, Figures 1–7, <http://links.lww.com/AA/B957>).

FINDINGS FROM STUDIES GROUPED BY CHRONIC PAIN SYNDROME

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 Treatment of CLBP includes the use of prescription medications such as acetaminophen, NSAIDs, ARIs, membrane stabilizers, and other miscellaneous nonopioids 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 Food and Drug Administration (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 2 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. Hickey⁸ enrolled a total of 30 patients into a study comparing diflunisal (500 mg twice daily) with acetaminophen (1000 mg 4 times daily) and found that diflunisal was superior in reducing pain scores compared to acetaminophen.

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

Abbreviations: ARI, amine reuptake inhibitor; FDA, Food and Drug Administration; NMDA, N-methyl-D-aspartate; NSAIDs, nonsteroidal anti-inflammatory drugs.

Nonsteroidal Anti-inflammatory Drugs. 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,⁹ diflunisal was not found to be superior to placebo for CLBP. 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 noninferiority of either celecoxib compared to diclofenac¹⁵ or piroxicam compared to indomethacin.¹⁴

Amine Reuptake Inhibitors. 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 al¹⁶ and Ward¹⁷ investigated comparative effectiveness of doxepin to desipramine in 2 separate studies and found that both doxepin and desipramine are effective in the treatment of CLBP, and in 1 of the studies, they found doxepin to be superior.¹⁶ Atkinson et al¹⁸ found that nortriptyline was superior to placebo for pain relief, 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 of 5 of them at the end point 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 al²⁹ investigated gabapentin versus inert placebo for CLBP and found that within each treatment arm, there was statistically significant reduction in pain, but when comparing gabapentin to placebo, there was no statistically significant difference in pain relief between the 2 groups. Two studies have investigated pregabalin compared to active control groups, and pregabalin was not found to be superior to opioids³⁰ or celecoxib³¹ for treatment of CLBP; however, celecoxib plus pregabalin was superior to monotherapy in the study by Romanò et al.³¹ Muehlbacher et al³² studied the effects of topiramate on CLBP compared to inert placebo and showed that topiramate was superior to placebo in reducing pain scores.

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,³³ 105 patients with CLBP were randomized to 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. In a study by Brown and Womble,³⁴ 49 patients with chronic spine pain were randomized to cyclobenzaprine, diazepam, or placebo for 2 weeks. 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 and the diazepam groups. Additionally, Basmajian³⁵ reported no difference in short-term reduction of pain and muscle spasms in CLBP patients between cyclobenzaprine and placebo after 18 days.

Mixed ARI/Opioid. Although tramadol and tapentadol have some activity at the μ -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 al⁴² found that tramadol/acetaminophen was not superior to placebo for CLBP. In a study comparing celecoxib to tramadol, O'Donnell et al⁴³ published that 200 mg celecoxib twice a day was superior to 50 mg tramadol 4 times a day in the relief of CLBP. 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 NSAIDs⁴⁷).

Topical Lidocaine Patch. A study by Hashmi et al⁴⁸ randomized 30 patients to either a 5% lidocaine patch or a placebo patch. 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. A study by Foster et al⁵⁰ involving 31 patients with CLBP being treated with botulinum toxin type A (BoNT-A) met criteria for inclusion. 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 Antagonists. In a study by Kleinböhler et al,⁵¹ it was found that in patients who received 100 mg amantadine, an N-methyl-D-aspartate (NMDA) antagonist compared to placebo over 1 week had no difference in pain rating scores at the end of the treatment period.

Miscellaneous. Tanezumab, a monoclonal antibody against nerve growth factor, is given intravenously and has been investigated in 2 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 end point⁵² and a 16-week pain outcome end point.⁵³

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 MPS is still unknown. Despite MPS being quite common, they are most often underdiagnosed 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).

Nonsteroidal Anti-inflammatory Drugs. Two studies were identified using injected or topical NSAIDs that met inclusion criteria. Frost⁵⁵ 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. Hsieh et al⁵⁶

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

Abbreviations: ARI, amine reuptake inhibitor; FDA, Food and Drug Administration; IM, intramuscular; NMDA, N-methyl-D-aspartate; NSAIDs, nonsteroidal anti-inflammatory drugs.

found that diclofenac sodium patch (60 mg) provided significantly superior pain relief compared to control patch after 8 days in patients with chronic myofascial pain of the upper trapezius muscle. No studies evaluating oral NSAIDs for chronic myofascial pain met criteria for inclusion.

Amine Reuptake Inhibitors. One study met inclusion criteria and studied the efficacy of fluoxetine versus amitriptyline for musculoskeletal pain. Schreiber et al⁵⁷ randomized 40 patients to either amitriptyline (50–75 mg/d) or fluoxetine (20 mg/d) for 6 weeks. 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,⁵⁸ 118 patients were either placed on 1500 mg methocarbamol 4 times a day or placebo for 1 week. After 1 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 al⁵⁹ 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. 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 al⁶⁰ reported that 5% lidocaine patch used for 14 days in cervical MPS may be superior to placebo, but the significant difference between the 2 groups

may have been skewed by an unexpected increase in pain in the placebo patch group.

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, and placebo.⁶² Neither study found that capsaicin patch provided superior pain control when analyzed to the comparator group.

Botulinum Toxin Type 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 Andrés et al⁶³ and found that BoNT-A was not superior in efficacy to placebo but was efficacious in a within-group analysis. There were 7 studies that showed superior efficacy of BoNT-A injections for cervical MPS compared to saline,^{64–68} local anesthetic and dry needling,⁶⁹ or steroid.⁷⁰ Eight published studies had negative findings in which 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 have been postulated to exist due to heterogeneous research design methodology and use of control procedures that are thought to produce analgesic benefits of their own.⁵⁴

Fibromyalgia

FM 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).

Nonsteroidal Anti-inflammatory Drugs. Two studies met inclusion criteria for this review. In the study by Yunus et al,⁸⁰ 46 patients with FM were randomized to either 600 mg ibuprofen 4 times a day or matched placebo for a total of 3 weeks. At the end of 3 weeks, pain rating scores between the 2 groups did not show superior efficacy for the ibuprofen group compared to the placebo group nor were there any within-group significant reductions in pain. Russell et al⁸¹ performed a 4-arm study investigating ibuprofen + alprazolam, ibuprofen + placebo, alprazolam + placebo, and placebo + placebo in 78 patients for 8 weeks. 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.

Amine Reuptake Inhibitors. A total of 29 studies were found to meet inclusion criteria and included studies on TCAs, SNRIs, and SSRIs. Milnacipran is an SNRI that is approved by the FDA for the treatment of FM, and 10 studies met criteria for inclusion in this review. Only one of these studies

Table 4. Fibromyalgia—Effective Medications Based on Included Studies

Fibromyalgia—Effective Medications	
FDA On-Label	Off-Label
NSAIDs	
None	None
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

Abbreviations: ARI, amine reuptake inhibitor; FDA, Food and Drug Administration; NMDA, N-methyl-D-aspartate; NSAIDs, nonsteroidal anti-inflammatory drugs.

by Staud et al⁸² had a negative finding between milnacipran and placebo groups; however, statistically significant reductions of small magnitude were noted within groups. Nine studies, many with large sample sizes, showed superior efficacy in pain reduction with milnacipran compared to placebo.^{83–91} Twelve studies evaluated duloxetine, an SNRI that is approved by the FDA for treatment of FM. Nine 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} Three studies reported nonsuperior efficacy of duloxetine to placebo: 1 studied a 30-mg dose^{101,102}; 1 studied a 60-mg dose; and 1 studied either a 60- or 120-mg dose.¹⁰³

Six studies investigated the efficacy of TCAs for the relief of pain in FM. Four studies showed efficacy of the TCA amitriptyline that was superior to placebo.^{104–107} Heymann et al¹⁰⁸ 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,¹⁰⁹ amitriptyline was not superior to placebo but had significant within-group reduction in pain scores.

Very few RCT studies have investigated the impact of SSRIs on pain in FM. Fluoxetine, an SSRI, was investigated in a study by Goldenberg et al¹⁰⁵ and was found to be superior to placebo when used in monotherapy or combined with amitriptyline. Controlled-release paroxetine has been investigated in a study by Patkar et al,¹¹⁰ whose findings indicate that it is superior to placebo for pain relief after 12 weeks of treatment in 116 patients.

Membrane Stabilizers. A total of 8 studies have been reported for pregabalin that met criteria for this review. Seven of these studies investigated pregabalin monotherapy at varying doses ranging from 150 to 600 mg/d and were found to have superior pain relief compared to placebo.

Arnold et al¹¹¹ and Mease et al¹¹² both found that daily total doses of 300/450/600 mg were all superior in pain efficacy to placebo. Crofford et al¹¹³ found that only 450 mg/d dosing was superior to placebo for pain efficacy (not at 150 or 300 mg/d). At doses of 300 or 450 mg/d, Ohta et al¹¹⁴ reported superior efficacy of pregabalin over placebo. Arnold et al¹¹⁵ and Clair and Emir¹¹⁶ also reported superior efficacy of pregabalin in pooled groups of pregabalin doses (300–450 mg/d) over placebo. Pauer et al¹¹⁷ published that only a modest statistically significant effect over placebo was noted at 450 mg/d (not at 300 or 600 mg/d). In a study by Gilron et al,¹¹⁸ 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.

Only one RCT investigating gabapentin was identified that met inclusion criteria. In this study by Arnold et al,¹¹⁹ 150 patients were randomized to either placebo or gabapentin (titrated to doses of 1200–2400 mg/d) for 12 weeks. 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 al¹²⁰ 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. Reynolds et al¹²² published a report showing that cyclobenzaprine was not superior to placebo in the treatment of FM pain.

In a study by Vaerøy et al,¹²³ a combination analgesic containing carisoprodol/cafeine/acetaminophen was compared to placebo for pain in FM in 58 female patients with FM over 8 weeks. No between-group comparisons are reported in the article; 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,¹²⁵ 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). 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 al¹²⁶ 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. 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 al¹²⁷ performed a randomized crossover placebo-controlled study in which 31 women with FM were placed on either oral low-dose naltrexone (4.5 mg/d) or placebo and followed for 16 weeks. 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 intravenous (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,¹³¹ 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. There was no improvement seen in patients taking prednisone versus placebo and, in fact, pain worsened with prednisone treatment over time.

Cannabinoids. Skrabek et al¹³² performed the one study on a cannabinoid for FM pain that met inclusion criteria. 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.

Postherpetic Neuralgia

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 older than 70 years with HZ have a 50% risk of developing PHN, whereas patients younger than 40 years 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 PC-RCTs^{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} and 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 3.4¹³⁴; similar percentages were observed in a subsequent PC-RCT, yielding an NNT of 3.6.¹³⁸ The pain reduction occurs within 1.5–3.5 days.¹³⁶ The minimal effective dose ranged from 150 to 200 mg/d,^{134–136} and the effect is dose dependent to 600 mg.^{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} and mood,^{139,140} and patient-¹³⁹ and clinician-¹³⁹ reported improvement in pain in PC-RCTs.

Table 5. Postherpetic Neuralgia—Effective Medications Based on Included Studies

Postherpetic Neuralgia—Effective Medications	
FDA On-Label	Off-Label
Topical (nonlocal anesthetic)	
Capsaicin 0.025%; 0.075%; 0.025%–10%–25%; 0.035%; 0.1%; 8%; 0.25%; capsaicin patch (8%)	None
ARI	
None	Amitriptyline, desipramine, nortriptyline, fluoxetine
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

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

The pain reduction occurs within 1¹⁴⁰ or 2¹³⁹ 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/d.¹⁴⁰ The gabapentin prodrug (gabapentin enacarbil, Pd-G) had a significant reduction in averaged 24-hour pain scores compared with placebo.¹⁴³ The minimum effective dosage was 1200 mg/d. Single daily administration of gastroretentive 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 are further challenged, as a third 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 subgroup 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

Amine Reuptake Inhibitors. 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 interference¹⁵² 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 PC-RCTs in Canada¹⁴²; 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 amitriptyline¹⁵² or nortriptyline.¹⁴⁹ The minimal effective dose ranged from 75 to 150 mg/d.¹⁵² Topical amitriptyline (2%) had no benefit compared to placebo.^{153,154}

In a single PC-RCT, fluoxetine¹⁵⁵ reduced the pain intensity of PHN but was less effective than desipramine. The minimal effective dose ranged from 20 to 60 mg/d.

Capsaicin. PC-RCTs for PHN were identified for high-dose (8%) topical capsaicin. It provided significantly greater pain relief and was more long-lasting (12 weeks) than control

(low-dose capsaicin, 0.04%), but this difference was modest in one study¹⁵⁶ 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, improved quality of life, and the patient's impression of relief.¹⁶⁰ The pain reduction occurs within 4 weeks after 4 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 IV 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,¹⁶⁹ and social and physical function.¹⁶⁹ Relief onset was within 14 days.¹⁶⁸ The average analgesic dose was 50–200 mg/d.¹⁶⁹

Nonsteroidal Anti-inflammatory Drugs. Cyclo-oxygenase-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 BoNT-A to painful skin has been shown to be effective in the reduction of pain intensity,^{173,174} improvement in sleep interference,^{173,174} and reduction in opioid use¹⁷³ 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 2 effective medications such as nortriptyline/gabapentin¹⁴² and morphine/gabapentin¹⁴¹ 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

The World Health Organization estimates that 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 (300 mg/d) has been shown to reduce “worst possible” pain intensity by 1.5 points (numerical rating scale) and 1.6 (visual analog scale) 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 an 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 150 mg/d¹⁸³ and 300 mg/d,^{184,185} but curiously patients in the lower

dose groups had a significant impression of improvement in their global well-being as compared to placebo.¹⁸³ Earlier comparative studies showed that 300 mg was similarly effective to 600 mg.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 clinician¹⁸⁷ reported improvement in pain, and hemodialysis-associated pruritus¹⁸⁸ 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 to 2400 mg/d.^{141,142,189,190} The Gr-G formulation of gabapentin,¹⁹¹ but not the gabapentin prodrug (gabapentin enacarbil, 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 mood¹⁹² in 2 PC-RCTs,^{192,193} but ineffective in all domains in 2 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/d.^{192,193}

Lamotrigine has been shown to be minimally effective in the reduction of pain intensity in 2 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/d, and pain reduction occurs within 6 weeks.

Oxcarbazepine has been shown to be borderline effective in the reduction of pain intensity¹⁹⁶ in a single PC-RCT, but no different in 2 PC-RCTs.^{197,198} The pain reduction occurs within 2 weeks.¹⁹⁶ The minimal effective dose in the single positive study was 1800 mg/d.¹⁹⁶

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

Amine Reuptake Inhibitors. Duloxetine has been shown to be effective in the reduction of pain intensity,^{200,201} the improvement in sleep interference due to pain,^{200,201} in quality of life,^{200,201} and patient-²⁰⁰ and clinician-²⁰⁰ reported improvement in pain and mood²⁰⁰ 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/d.^{200,202} No difference was noted between 60 mg and 120 mg/d.²⁰¹ Longer-term studies showed maintenance of pain relief to 6 months²⁰⁶ and 1 year.²⁰⁷

Table 6. Painful Diabetic Neuropathy—Effective Medications Based on Included Studies

Painful Diabetic Neuropathy—Effective Medications	
FDA On-Label	Off-Label
Topical (nonlocal anesthetic)	
Capsaicin 0.025%; 0.075%; 0.025%–10%–25%; 0.035%; 0.1%; 8%; 0.25%	Clonidine
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

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

Venlafaxine has been shown to be effective in the reduction of pain intensity and patient- and clinician-reported improvement in pain in PC-RCTs.²⁰⁸ The pain reduction occurs within 2²⁰⁹ or 6²⁰⁸ weeks, and the NNT was 4.5.²⁰⁸ Similar efficacy results have been reported in other small PC-RCTs.²⁰⁹ The minimal effective dose ranged from 150 to 225 mg/d.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 to 150 mg/d,^{212,213} and the effects of amitriptyline were dose dependent to 150 mg/d.²¹³

Paroxetine,²¹⁶ but not fluoxetine,²¹⁰ reduces the pain intensity of DPN, improves sleep interference, and improves 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 to 50 mg/d.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 4 times per day of 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 experienced small size. One trial noted improvement in sleep interference and nocturnal pain at high doses (675 mg/d),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/d.^{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 al²²⁷ reported improvement in pain in PC-RCTs. The pain reduction occurs within 2–3 weeks.²²⁷ The minimal effective dose ranged from 100 mg/d.^{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 210 mg/d.

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 and 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 painful feet produces 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 2 effective medications such as nortriptyline/gabapentin¹⁴² and morphine/gabapentin¹⁴¹ 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.

Radicular Pain

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%–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 RP 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

Table 7. Radicular Pain—Effective Medications Based on Included Studies

Radicular Pain—Effective Medications	
FDA On-Label	Off-Label
Topical (nonlocal anesthetic)	
None	None
ARI	
None	Duloxetine, milnacipran, amitriptyline
Membrane stabilizers	
None	None
ARI/opioid	
None	None
Local anesthetics	
None	None
NMDA antagonists	
None	None
Miscellaneous	
None	Indomethacin

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

RCT (Methods section lacks sufficient detail to definitively determine) and suffers from trial design flaws reported a modest benefit of pregabalin for L5 RP but not for lower nerve root distribution RP.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

Amine Reuptake Inhibitors. 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 RP compared to placebo, but no secondary outcome such as quality of life, mood, or physical function were improved.²⁴²

Amitriptyline, at 25 mg/d,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

Nonsteroidal Anti-inflammatory Drugs. Indomethacin was found to be effective in the reduction of chronic RP in a PC-RCT,²⁴⁵ but not others.²⁴⁶

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 al²⁴⁷ in 1981, Veldman et al²⁴⁸ in 1993, and van de Beek et al²⁴⁹ in 2002, 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 criteria²⁵⁰ 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 specificity²⁵³ and is therefore recommended in both clinical and research settings.²⁵⁴ There are 2 types of Budapest criteria, a clinical and a research diagnostic criteria.

Only articles that used the Budapest or IASP criteria to diagnose CRPS were included except 2 articles on bisphosphonates that used the criteria by Kozin et al.²⁴⁷ These 2 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 articles that used the older criteria^{248,249} other than the one by Kozin et al²⁴⁷ and studies on IV regional or neuraxial treatments.

Ketamine. A study showed IV ketamine to have significantly better pain relief when compared to placebo²⁵⁵ (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 µg/kg min (approximately 5 mg/h for a 70-kg patient) to a maximum of 7.2 µg/kg min (30 mg/h for 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 placebo²⁵⁶ 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 CRPS²⁶⁴ (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.²⁶⁵ 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 IV route was also noted to be significantly better than placebo.²⁵⁷

A single IV infusion of 60 mg pamidronate resulted in improvements in pain scores, patient's global assessment of disease score, and functional assessment (Table 8).²⁵⁸ IV clodronate, 300 mg, given daily for 10 consecutive days was noted to have better results (pain scores, clinical global assessment) over placebo.²⁵⁹ Neridronate was also noted to be significantly better than placebo in a multicenter trial.²⁶⁰ The dose was 100 mg neridronate given 4 times over 10 days; improvements were noted with regard to pain on passive motion, McGill Pain Questionnaire, and SF-36. None of the patients had CRPS at 1 year follow-up.

IV Immunoglobulin. The possibility that immune mechanisms are involved in the pathogenesis of CRPS led investigators to examine the effect of IV 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.²⁶¹ Their findings led the authors to proceed to a PC-RCT²⁶² (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/d, total dose of 0.5 g/kg) or placebo. The intervention was given for 2 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 ($P < .001$); the average pain intensity was 1.6 less after the IVIG treatment and no adverse effects were noted.

IV Magnesium. Two studies examined the effect of IV magnesium on CRPS.^{268,269} One study involved 10 patients, 8 received the IV magnesium, while 2 were given saline.²⁶⁸ The

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 ²⁵⁵ ; 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 wk, gone at 12 wk	Nausea, vomiting, psychotomimetic effects (drug high, hallucinations)
Schwartzman et al ²⁵⁶ ; IASP criteria; P, R, DB, PC	Ketamine infusion for 4 h × 10 d; 0.35 mg/kg/h not to exceed 25 mg/h (100 mg over 4 h); 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 4 h) gave greater and longer relief	Nausea, tiredness, dysphoria, headache (midazolam and clonidine given during infusion)
Adami et al ²⁵⁷ ; Kozin criteria; P, R, DB	Alendronate, 7.6 mg in 250 mL saline versus saline infusion daily × 3 d 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 ²⁵⁸ ; IASP criteria; P, R, DB	Pamidronate 60 mg as a single infusion versus 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)
Varennna et al ^{259,260} ; Kozin criteria; P, R, C, DB	Clodronate 300 mg daily × 10 consecutive days versus 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
Varennna et al ^{259,260} ; Budapest criteria; P, R, C, DB	Neridronate, 100 mg given 4 times over 10 days versus 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 d: Fever, chills sweating, postural hypotension, nausea, vomiting, diarrhea, lethargy, anxiety, restlessness, sleep disturbance, headache. Signs and symptoms of anaphylactoid reaction (nasal congestion, itch, wheeze, exanthema) none needing treatment
Goebel et al ^{261,262} ; Budapest criteria; P, R, DB, C	IVIg, total dose of 0.5 g/kg (0.25 g/kg/d) versus 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 ²⁶³ ; IASP criteria, P, R, DB, PC	Infliximab, 5 mg/kg given at 0, 2, 6 wk; 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

Abbreviations: C, crossover; CRPS, complex regional pain syndrome; 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 ²⁶⁵ ; Budapest criteria; P, R, PC, DB, C	Alendronate, 40 mg orally daily × 8 wk versus 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 ²⁶⁶ ; IASP criteria; P, R, DB, PC, C	Gabapentin × 3 wk, titrated to 600 mg TID versus placebo, 2 wk washout, then 3 wk 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 ²⁶⁷ ; Budapest criteria; P, R, PC	Tadalafil, 10 mg for 4 wk then 20 mg for another 84 versus placebo; 24 patients, 12 per group	Nonstatistically 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

Abbreviations: C, crossover; CRPS, complex regional pain syndrome; DB, double-blind; IASP, International Association for the Study of Pain; P, prospective; R, randomized.

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 2 patients who had saline were not presented or analyzed and the results between the 2 treatments were not compared. The same group of investigators later performed a PC-RCT.²⁶⁹ Fifty-nine patients with CRPS type I criteria were randomized into either IV magnesium (29) or placebo (27).²⁶⁹ 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 1.²⁶⁹

IV Mannitol and IV Parecoxib. A study compared mannitol, an oxygen radical scavenger with placebo.²⁷⁰ The investigators noted that 10% mannitol in 1 L, 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 2 consecutive days, with saline²⁷¹ 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^{272,273} or piroxicam.²⁷⁴ However, the studies were hampered by the use of physical and radiological findings to diagnose CRPS^{272,274} or use of the criteria by Kozin et al.^{247,273} 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.²⁷⁵ 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 placebo²⁶⁶ (Table 9). The dose of gabapentin was started at 600 mg daily then titrated to 600 mg TID, treatment was for 3 weeks followed by a 2-week washout before the crossover portion of the study of another 3 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.²⁷⁶ 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.²⁷⁷ This led investigators to compare morphine (30 mg daily) with or without memantine (40 mg daily) in a PC-RCT.²⁷⁸ The authors showed that only the combination reduced the pain and disability. Unfortunately, the authors used the criteria by van de Beek et al²⁴⁹ to diagnose CRPS.

Tadalafil. Tadalafil inhibits phosphodiesterase-5, relaxes smooth muscle, and causes vasodilatation reversing decreased regional blood flow in CRPS. A PC-RCT showed a nonstatistically different temperature change.²⁶⁷ 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.^{279–283} Two PC-RCT studies on nasal calcitonin showed conflicting results, one noted superiority of calcitonin,²⁷⁹ while the other did not.²⁸⁰ One study used the criteria by Kozin et al²⁴⁷ while the other based their diagnosis only on the presence of swelling and stiffness after a Colles fracture.²⁸⁰ Another randomized study on nasal calcitonin was single-blinded and based their diagnosis on clinical symptoms and physical examination findings; the authors noted no difference between nasal calcitonin to paracetamol.²⁸² Two studies on parenteral calcitonin are not discussed because one study was not blinded,²⁸¹ while randomization or blinding was not discussed in the other study.²⁸³ In summary, one randomized trial showed superiority of calcitonin over placebo,²⁷⁹ while 2 randomized trials showed improvements but no superiority over placebo²⁸⁰ or paracetamol.²⁸² 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. Dimethyl sulfoxide (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 2 months, was significantly better than placebo in patients with acute reflex sympathetic dystrophy (RSD).²⁸⁴ Improvements were noted in RSD scores and pain relief at 2-month follow-up. Another study was a randomized, double-dummy controlled trial that compared DMSO with *N*-acetylcysteine, another free radical scavenger.²⁸⁵ The investigators showed improvements but with equal efficacy between the 2 drugs. Unfortunately, both studies diagnosed RSD with the 1993 criteria by Veldman et al.²⁴⁸

Botulinum Toxin Type 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.²⁸⁶ 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.²⁸⁶

Tumor Necrosis Factor- α Inhibitors. A study noted the lack of superiority of infliximab, 5 mg/kg given at weeks 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).²⁶³

CONCLUSIONS

The scope of this review on nonopioid 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 that 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 Digital Content 3, Table 1, <http://links.lww.com/AA/B958>). The effect sizes for many treatments were small, including some of those that are FDA approved. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (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 they 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 nonopioid medications for chronic pain conditions. For CLBP, nonopioid 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, BoNT-A, and tanezumab.

For patients with MPS, 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 BoNT-A. FM has been well studied, and the following nonopioids 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 PHN, significant positive findings with regard 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 BoNT-A. In PDN, the following nonopioid medications have proven beneficial to improve pain scores: membrane stabilizers (pregabalin, gabapentin,

topiramate, lamotrigine, oxcarbazepine, and zonisamide), ARIIs (duloxetine, venlafaxine, desipramine, imipramine, amitriptyline, and paroxetine), topical capsaicin, local anesthetics (mexiletine), NMDA antagonists (dextromethorphan), mixed ARI/opioid (tapentadol extended-release and tramadol), BoNT-A, cannabinoids (inhaled cannabis and nabilone), and topical clonidine. Nonopioid medications found to be effective for pain relief in RP are ARIIs (duloxetine, amitriptyline, and nortriptyline) and NSAIDs (indomethacin). Finally, for CRPS, 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 (eg, 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 nonmalignant chronic pain syndromes. Instead, we chose to include the most common noncancer 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 that 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 CLBP 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 the 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. Second, 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 US adults in which 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 mechanism-based treatments for the chronic pain syndromes discussed in this review. Studies in which a long-term follow-up is 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 is needed to determine whether incremental or synergistic benefits are seen and whether or not these are sequence reliant. Maintaining rigorous methodology in which the same outcome measures following IMMPACT recommended guidelines (pain outcome measures, quality of life measures, and functioning measures) would likely allow for better consistency and reproducibility, which are of utmost importance in guiding evidence-based care. ■■

DISCLOSURES

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Contribution: This author helped collect data and prepare the manuscript.

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Contribution: This author helped collect the data and prepare the manuscript.

Conflicts of Interest: Robert W. Hurley is currently affiliated with the Department of Anesthesiology and the Clinical Translational Institute, Medical College of Wisconsin (MCW), Milwaukee. He received a 2016 to 2017 grant from the Clinical Translational Research Institute (MCW) (Josh Field, PI; Robert Hurley, co-investigator) functional magnetic resonance imaging in Sickle Cell Disease Pain (\$50,000; 2015–2020 AHRQ R01) from the Agency for Healthcare Quality and Research (Chris Harle, PI; Robert Hurley, co-investigator), Designing User-Centered Decision Support Tools for Primary Care Pain Management (\$1,943,756; 2015–2016) Faye McBeath Foundation (PI), reducing the transition from prescription opioid abuse to heroin abuse through clinical provider education, \$50,000; 2013–2016 Pfizer, Inc (PI; Christopher Harle, co-PI); An Integrative and Sustainable Approach to Pain Management in Primary Care, \$499,997; 2015–2016 St Jude Medical, Education of Multidisciplinary Pain Fellows (PI) MCW; 2015–2016 Medtronic Inc, Education of Multidisciplinary Pain Fellows (PI) MCW; 2014–2015 Boston Scientific, Education of Multidisciplinary Pain Fellows (PI) UF; 2014–2015 Medtronic, Education of Multidisciplinary Pain Fellows (PI) UF.

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