Multimodal Treatment of Chronic Pain

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KEYWORDS

- Multimodal
- Combination therapy
- Chronic pain treatment
- Multidisciplinary chronic pain treatment
- Interdisciplinary pain treatment

KEY POINTS

- Most patients with chronic pain receive multimodal treatment.
- Combination pharmacotherapy should be carefully selected to avoid additive side effects and drugs with similar mechanisms of action or other interactions while still providing benefit.
- Structured interdisciplinary programs that include psychological treatments, rehabilitation, and medical management are beneficial yet costly, and may be applicable to only a minority of patients.
- Interventions including surgery and injections should rarely be first-line treatments and should be combined with other domains—rehabilitation, pharmacotherapy, attention to mental health, and coping.
- Complementary and alternative medicine as an addition to conventional pain treatment is a safe yet largely understudied area.

INTRODUCTION

Chronic pain of all sorts is not only responsible for considerable personal suffering worldwide, it also contributes to substantial costs to society. Although suffering cannot be quantified, the economic burden of pain in the United States alone is estimated at $650 billion per year in health care and lost productivity.\textsuperscript{1} Although there are many treatment options available, none are universally endorsed, and many come with counterproductive side effects, or in the case of interventions, may lead to further complications.
When treating chronic pain, a common goal is to provide a lasting and meaningful reduction in suffering with concomitant improvements in overall functioning and health-related quality of life. Additional considerations are to minimize side effects and adverse events, and to deliver the care in a cost-effective manner. Ongoing pain is multidimensional with physical, cognitive, psychological, and behavioral aspects. Given the complex nature of chronic pain and the goals for treating it, it is not surprising that any 1 treatment by itself is rarely adequate to achieve these objectives. Rather, chronic pain lends itself to a multimodal treatment approach (Fig. 1). Treatment often includes medication(s), physical rehabilitation, lifestyle changes, psychology, advanced pain interventions, surgery, and complementary and alternative medicine in various combinations. Combination, multimodal therapy can be on an ad hoc basis, come about as an evolution in patient care owing to partial or incomplete treatment response, or take place in a more formalized setting such as a structured rehabilitation program. Although combination therapy is commonplace in clinical practice, such approaches are very little studied. In this article, we review multimodal, combination therapy for chronic pain.

**PHARMACOLOGIC TREATMENT**

With ongoing chronic pain, it is unusual for a single medication to result in satisfactory pain relief in a unimodal, stand-alone fashion. Therefore, combination pharmacologic treatment is an important aspect of multimodal chronic pain management. A key component of treating pain with medications is finding the balance between effective treatment and acceptable side effects (Fig. 2).

“Effective treatment” is difficult to define, because it will almost never mean a complete remission of pain. An analysis from a collection of industry-sponsored chronic pain trials suggest that a reduction of pain by 30% is clinically meaningful, because it is at this level that patient ratings demonstrate a “much improved” pain experience.\(^2\)

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**Fig. 1.** Many targets need more than 1 arrow.
Many of the pharmacologic agents used to treat chronic pain are central nervous system depressants and may impair the patient’s energy, mobility, memory, and ability to exercise, all of which are crucial for successful rehabilitation. Although the mechanisms behind chronic pain vary and are poorly understood, it is generally characterized by a heightened sensitivity and hyperexcitability of the nervous system, which may be amenable to treatment with anticonvulsants and antidepressants, as well as opioids. To minimize sedation caused by a single pharmacologic agent, a reduction in dose is often desired, but this dose reduction may come at the cost of lessened analgesic effects. Ideally, the addition of a second agent would have an additive analgesic effect, but not a cumulative side effect profile, allowing the practitioner to use the lowest dose possible without losing analgesia and minimizing side effects. The use of combination pharmacotherapy has a wide evidence base in acute pain and so the rational that it may work for chronic pain as well is not unfounded.3

**THEORY BEHIND COMBINED PHARMACOLOGIC TREATMENT**

Studies have shown that, at best, most medications give a positive response in only a small percentage of people.4 So until new more effective medications are developed, there is a need to identify medications that work well in combination. Another rationale for combination drug therapy (CDT) is to target the different pain mechanisms that contribute to the patient’s overall pain syndrome. For example, a patient with chronic neck pain may have both a neuropathic as well as inflammatory component to their pain and may benefit from a combination therapy that targets each of these components. In clinical practices, this in fact seems to be a common perception. Recent studies show that more than one-third to one-half of chronic pain patients are taking more than 1 analgesic.5–7 Unfortunately, some studies show that certain combinations of medications cannot only worsen the side effect profile, but have no synergistic analgesic effect at all.8,9 There is a glaring need for further research to identify first-line combination pharmacotherapy for specific chronic pain conditions to guide practitioners in a rational approach to the medical treatment of patients with chronic pain (Table 1).
There are a number of ways to approach the available information on CDT for chronic pain. We have organized this section by type of pain.

Neuropathic Pain

The International Association for the Study of Pain defines neuropathic pain as, “Pain caused by a lesion or disease of the somatosensory system.” This includes central disorders (eg, spinal cord injury pain, multiple sclerosis pain, poststroke thalamic pain) as well as peripheral disorders (eg, diabetic neuropathy, postherpetic neuralgia, and tic douloureux) A number of studies explore CDT for neuropathic pain. One such successful combination is a gabapentinoid together with a tricyclic antidepressant. Both tricyclic antidepressants and gabapentinoids are proposed as first-line agents for neuropathic pain. These medications have completely different mechanisms of actions (gabapentinoids are alpha-2-delta calcium channel modulators and tricyclic antidepressants have multiple mechanisms of action, including norepinephrine and serotonin reuptake inhibition), and so are logical candidates for combination therapy. This CDT has been studied in the treatment of diabetic peripheral neuropathy and postherpetic neuralgia and was found to be more effective than either drug given alone. However, a 2012 Cochrane review looked at the combination pharmacotherapy for neuropathic pain and concluded that many 2-drug combination therapies demonstrate superior efficacy than either drug alone, but that limited trial size and the short duration of the studies precluded them from making recommendations for any 1 specific recommendation for neuropathic pain.

Arthritis

Rheumatologic conditions associated with ongoing pain have a strong peripheral nociceptive component, although recent data suggest a component of central sensitization in many patients, as evidenced by limited correlation between pain complaints and disease severity. There have been a number of studies evaluating successful CDT in arthritis. Tramadol mixed with acetaminophen and/or a nonsteroidal anti-inflammatory drug is 1 example that was found to be efficacious. Again, however, a Cochrane review was preformed in 2011 for inflammatory arthritis, and they found the studies available for review had inadequate study design, were industry funded,
or were dated before the advent of disease-modifying antirheumatic drug therapy. Because of this, they were unable to make any recommendations.19

**Back Pain**

Back pain is among the most common (if not the most common) chronic pain conditions, but despite this, a recent systemic review of CDT for this condition only found 6 studies eligible for review.20 Chronic low back pain has been shown to be secondary to both neuropathic as well as nociceptive pain mechanisms.21 This mixed pain picture lends itself to multimodal pharmacologic treatment. Studies examining the combination of an opioid and acetaminophen22–24 found the combination to be beneficial. However, one must proceed with caution when prescribing opioids for chronic low back pain, because opioids are associated with significant risk and no long-term studies support their use. A 2013 Cochrane Review looked at opioid use in chronic back pain and found very low to moderate quality of evidence in their short-term use for pain and function.25 One of the examined trials found no difference when comparing tramadol with a nonsteroidal anti-inflammatory drug.26 Another trial examined in the review compared nortriptyline with morphine to the combination of the 2 to an active placebo and found that none of the treatments were effective.8

**Fibromyalgia**

Because of the physiologic, behavioral, and social issues that often surround patients with fibromyalgia, it is a complicated condition to treat. Our current understanding of fibromyalgia leads us to believe that it is mainly a centralized pain disorder with widespread pain as its defining feature. It is often accompanied by fatigue, sleep disturbance, and memory and mood difficulties. With successful treatment, several of these symptoms will typically improve.27 When treating a polygenic chronic illness such as this, how does one decide on an appropriate CDT without exacerbating the central nervous system depressant components of the disease? Studies looking into CDT for fibromyalgia are limited. Positive CDT trials include the combination of tramadol and acetaminophen,28 cyclobenzaprine plus fluoxetine,29 pregabalin added to either quetiapine or trazodone,30 and fluoxetine and amitriptyline.31 However, the study evaluating tramadol and acetaminophen was industry sponsored and short term (13 weeks). It also did not include a group evaluating tramadol or acetaminophen alone. Since that study was published, other studies have found chronic opioids to be of little benefit, if not detrimental, to overall functioning in patients with fibromyalgia.32,33 The study evaluating fluoxetine paired with amitriptyline was also short, with a limited number of study participants and the effects were modest. Clearly, there is a need for further trials.

That being said, when presented with a patient suffering from fibromyalgia, who has received only partial benefit from monotherapy, it may be prudent to try CDT. Calandre and colleagues34 suggests starting with the US Food and Drug Administration–approved drugs pregabalin, duloxetine, and milnacipran. Begin by carefully evaluating the patient’s symptoms and matching the CDT with the desired effects. Addition of a third drug, or a drug that is, not US Food and Drug Administration approved such as trazodone or quetiapine, may be desired. As always, careful titration and avoidance of drugs with similar mechanisms or dangerous synergistic side effects is important.

**PSYCHOLOGICAL APPROACHES**

Ongoing pain is commonly complicated by sleep interference, mood disturbances, maladaptive behaviors, and ineffective coping strategies, making psychological
interventions a logical treatment component. However, many studies examining cognitive–behavioral therapy (CBT) and other mental health approaches as stand-alone treatment demonstrate only modest impact on pain, mood, or function. Currently CBT is the first-line psychological treatment for chronic pain. CBT focuses on the reduction of disability by emphasizing patient coping, adaption, and self-management. It teaches the patient skills such as relaxation, activity pacing, and identification and elimination of negative appraisals, fear avoidance, and catastrophizing. CBT has been shown to be helpful for pain, depression, anxiety, and insomnia. Similar to other pain management modalities, treatment effects of CBT have been shown to be only modest. Again, this highlights the need for a multi-modal approach.

One likely combination is CBT paired with pharmacologic management. Calderon Pdos and colleagues did a small pilot study on the combination of amitriptyline with CBT in patients with temporomandibular joint pain and found no differences between groups. However, the authors thought that this was owing to a number of weaknesses in the study design. Monticone and colleagues performed a study comparing CBT combined with exercise versus exercise alone in patients with low back pain and found that the combination group had longer lasting improvement in fear avoidance, reduced disability, and pain.

INTERVENTIONS

Often, radicular pain leads to a referral to an interventionalist, be it a surgeon or a pain specialist. This often leads to an epidural steroid injection, facet procedures, other injections, or surgical intervention. Nonsurgical interventional techniques are among the major modalities contributing to the increasing costs of treating chronic pain patients in the United States. In fact, epidural steroid injections are the most commonly performed procedure in the United States, yet evidence is controversial and inconclusive as to their long-term effectiveness. Similarly, most randomized studies evaluating the effectiveness of neurosurgical interventions for neuropathic pain have found minimal long-term benefits. These results are perhaps because we have not been able to match patients with the correct treatment, or because patients with ongoing pain often have multiple components to their pain and suffering that do not lend themselves to a single treatment modality. Perhaps a combination of treatments, tailored to a particular patient’s need, would be more beneficial. For example, surgery might play a greater role in a patient with serious neurologic symptoms, whereas epidural steroid injections may work better for patients with ongoing inflammatory pathology, and patients with ectopic nerve impulses stemming from central sensitization or chronic nerve injury may respond better to pharmacotherapy.

Recently, Cohen and colleagues performed a randomized study comparing the effectiveness of epidural steroid injections, conservative treatment, or combination treatment in patients with cervical radicular pain. They found that patients in the conservative group receiving gabapentin or nortriptyline or both along with physical therapy fared the same as patients in the epidural steroid injection group. The patients in the combination group fared slightly better on some outcome measures, but most differences were not significant. Until further studies have elucidated patient selection criteria, the take home message with regard to interventions is that owing to the risk/benefit ratio, interventional and operative techniques should not be first-line treatments. This sage advice goes for many common interventional procedures, including sacroiliac joint injections, medial branch blocks, and radiofrequency ablative procedures.
INTERDISCIPLINARY PAIN REHABILITATION PROGRAMS

Research trends indicating that chronic pain is best understood as a combination of physical, psychological, and social interactions has led us to the current “bio-psychosocial” treatment paradigm. Interdisciplinary pain rehabilitation programs that target all of these aspects of a patient’s pain have been developed to address this need and are the ultimate in multimodal pain treatments. Interdisciplinary pain rehabilitation programs do not have a standardized format, but as a whole, offer coordinated care between physicians, psychologists, physical therapists, and other health care providers in either an inpatient or outpatient setting. Often, rehabilitation programs are a last ditch attempt after all other alternatives have been proven insufficient. There have been a number of positive studies to assess the efficacy of multi-component therapy in this population often regarded as “treatment resistant.”

Fibromyalgia

Both the American Pain Society and the German guidelines for the management of fibromyalgia give strong recommendations to multicomponent therapy. A 2009 meta-analysis for multicomponent treatment in fibromyalgia found that, although there is limited evidence for long-term effects, there is strong evidence for reduction of symptoms in key areas of fibromyalgia syndrome such as pain, fatigue, depression, and physical fitness.41

Chronic Low Back Pain

A 2014 Cochran Review analyzed multidisciplinary biopsychosocial rehabilitation programs for low back pain and found moderate quality evidence that multidisciplinary biopsychosocial rehabilitation treatment results in modest improvements (1 point out of 10) for pain when compared with usual care or physical therapy alone, and that it doubled the likelihood that people were able to return to work in the next 6 to 12 months.42 They emphasized the need to weigh the cost–benefit ratio as well as the time–benefit ratio when considering enrolling a patient in such a program.

COMPLEMENTARY AND ALTERNATIVE MEDICINE AND SELF-MANAGEMENT

For no lack of effort, conventional treatment of chronic pain is lacking in many aspects. Intolerable side effects, serious risks, and lack of efficacy have led many patients to seek complimentary and alternative medicine and self-management strategies such as acupuncture, relaxation, yoga, message therapy, and biofeedback.43 A recent review of the literature behind such treatments was able to find evidence in favor of use of yoga, tai chi, and music therapy for self-management of pain, but was unable to find quality evidence to support any other common complementary and alternative medicine modalities.44 This was mainly owing to the fact that there is a dearth of quality randomized control studies available, and not because the evidence points away from these modalities as being effective. In 2014, Lee and colleagues43 performed a review looking at multimodal integrative therapies for chronic pain, and came to a similar conclusion. There is not enough high-quality research to make a recommendation regarding multimodal integrative therapies for chronic pain.

SUMMARY

Combination therapy for the treatment of chronic pain remains an important and common, yet understudied, approach. The development of refined clinical strategies to predict positive outcomes and to optimize individualized combination therapy is the
goal for future improvements. Until more information becomes available, a prudent and rational approach with careful attention to the potential risks and monitoring for patient improvement is vital.

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