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Combination Drug Therapy for Chronic Pain: A Call for More Clinical Studies

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Summary

Chronic pain is a debilitating clinical condition associated with a variety of disease entities including diabetic neuropathy, postherpetic neuralgia, low back pathology, fibromyalgia, and neurological disorders. For many general practitioners and specialists, managing chronic pain has become a daunting challenge. As a modality of multidisciplinary chronic pain management, medications are often prescribed in combinations, an approach referred to as combination drug therapy (CDT). However, many medications for pain therapy, including antidepressants and opioid analgesics, have significant side effects that can compound when used in combination and impact the effectiveness of CDT. To date, clinical practice of CDT for chronic pain has been based largely on clinical experiences. In this article, we will focus on 1) the scientific basis and rationales for CDT, 2) current clinical data on CDT, and 3) the need for more clinical studies to establish a framework for the use of CDT.

Keywords

Chronic pain; Neuropathic pain; Fibromyalgia, Multimodal; Polypharmacy, Drug therapy; Clinical trial

Introduction

Enormous challenges exist in the management of chronic pain resulting from nerve injury, diabetic neuropathy, postherpetic neuralgia, low back pathology, fibromyalgia, endometriosis, arthritis, neurological disorders (e.g., multiple sclerosis, Parkinson's disease), and malignancy. First, pain experience varies among individuals with regard to its intensity and quality^{18,78-80} and is influenced by an array of biological and psychosocial factors^{12,38}. Second, the self-reporting of pain, the primary method by which patients communicate with healthcare providers, often correlates poorly with the severity and

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duration of underlying pathological conditions. Third, confounding factors such as adverse effects from pain therapy itself complicate clinical pain diagnosis and outcome assessment^{8, 64}. While managing chronic pain requires multidisciplinary approaches including interventional procedures, physical rehabilitation, and cognitive behavioral therapy, drug therapy often plays an important role in the clinical setting. Many general practitioners and specialists (e.g., neurology, rheumatology, oncology, gynecology, and pain medicine) have regularly employed combination drug therapy (CDT) for symptomatic pain relief in the absence of data to guide the combinations used²⁵.

It has long since been considered that drug therapy should ideally be based on the mechanisms underlying clinical pain presentations¹⁰⁶. For example, anticonvulsants may be beneficial for relieving pain caused by injured nerve fibers^{61, 96}. Although a mechanism-based approach for drug therapy has its merit, the incomplete understanding of pain mechanisms, the dearth of medications with sufficient target specificity, and significant barriers to translational research^{15, 64, 84} have so far kept the promise of this goal out of reach. To date, clinical practice of CDT for chronic pain has been based largely on clinical experiences due to the lack of information regarding the choice of pain syndrome-specific drug combinations. In this article, several key issues concerning CDT will be discussed with the emphasis on 1) the scientific basis and rationales for CDT, 2) current clinical data on CDT, and 3) the need for more clinical studies to establish a framework for clinical practice of CDT.

Rationales for CDT

Is there a scientific basis for CDT in chronic pain management? Evidence from two convergent lines of preclinical and clinical investigation (pharmacological interaction and complexity of chronic pain mechanisms) suggests that CDT may be both necessary and justified.

Pharmacological interaction

Traditional pharmacological approaches are often used to balance the efficacy and side effect of a drug therapy. While CDT may be used to influence the pharmacological properties (i.e., kinetics and dynamics) of a compound, which may ultimately impact efficacy, a useful therapeutic focus within the context of chronic pain management is how to maximize therapeutic efficacy while minimizing deleterious side effects. Two general approaches are often used to address this issue.

The first approach is based on the notion that two compounds (e.g., NSAID and opioid analgesic) may have additive effects if they target complementary pathways or mechanisms of a common clinical condition. Thus, it is possible to obtain the same pharmacological effect with two compounds each at a lower dose than is necessary to produce the same effect with either compound alone, thereby minimizing side effects associated with either compound. Because some compounds may have potential supra-additive (synergistic) effects (e.g., gabapentin and opioid analgesic), both the dose-sparing effect and potential enhancement of therapeutic efficacy associated with a drug combination may be substantial^{33, 40}. The second approach to minimize side effects is with a drug combination in which at least one of the drugs is included specifically to counter side effects of another drug in the combination (e.g., diclofenac and misoprostol)²¹.

Complexity of chronic pain mechanisms

The generation of pain following tissue injury involves four basic processes (Fig. 1): 1) *transduction* (converting noxious stimulation from tissue injury to nociceptive signals), 2) *transmission* (sending nociceptive signals in the form of action potential from the site of

tissue injury to the spinal cord and brain), 3) *plasticity* (amplification or inhibition of nociceptive signals as a result of injury-induced changes in the nervous system manifest at multiple levels, such as the emergence of ectopic activity from the dorsal root ganglion and alterations in synaptic transmission and descending modulatory circuitry), and 4) *perception* (pain experience). Of note, although some drugs (e.g., NSAID, acetaminophen, topical lidocaine) reduce pain through selectively modulating the nociceptive processing, other drugs (e.g., opioid analgesic, antidepressant) may have a more complex effect on both the nociceptive processing and pain perception.

Recent preclinical research suggests that the mechanisms of chronic pain are much more complex than those of acute postoperative pain, and may be influenced by a number of factors including: a) type of injury (e.g., distinct ion channels or ion channel phenotypes underlie pain associated with nerve injury versus transient tissue inflammation⁴¹), b) site of injury (e.g., distinct mechanisms underlie visceral versus somatic pain⁴¹), c) “history” of the injured tissue (e.g., differential tissue responses to subsequent injury versus responses in “naïve” tissue⁴⁵), d) developmental as well as age dependent changes in pain mechanisms⁴¹, and e) genetic as well as sex/gonadal influences, both on the manifestations of chronic pain and the sensitivity to various therapeutic interventions^{22, 45}. Moreover, the development of clinical comorbidities such as depression and sleep disorders is also the rationale for the use of CDT in the clinical setting⁷³.

Emerging concepts on clinical necessity and feasibility of CDT

Several emerging concepts highlight the clinical necessity and feasibility of CDT. First, viable therapeutic targets for acute pain may no longer be effective as pain persists^{20-23,75}, and a variety of changes at the cellular and system level associated with chronic pain may impact the efficacy of drug therapy as demonstrated in preclinical studies⁴⁶. For example, some of these changes, such as increase in the expression of cyclooxygenase-2 (COX-2), may contribute to an increase in therapeutic efficacy (e.g., NSAIDs or COX-2 inhibitors)⁸⁹, whereas others, such as an increase in glucocorticoid receptor activation, could contribute to a decrease in therapeutic efficacy (e.g., opioid analgesics)⁵⁹. Second, the role of central sensitization may serve as a common mechanism for several seemingly unrelated chronic pain conditions (e.g., fibromyalgia, complex regional pain syndrome, and irritable bowel syndrome) although not all clinical pain conditions may have a clearly identifiable source of peripheral nociceptive input that drives the mechanisms of central sensitization. Therefore, medications such as pregabalin and duloxetine capable of influencing the mechanisms of central sensitization could be beneficial under these circumstances^{1,31}. Third, those seemingly redundant cellular pathways of chronic pain mechanisms may serve as a means to amplify nociceptive signals but also provide potential therapeutic targets for CDT (Fig. 1). For instance, treatment of neuropathic pain could include a) sodium channel blockers to reduce spontaneous and ectopic activity^{3,54}, b) calcium channel blockers to counter nerve injury-induced changes in calcium channel subunit function¹⁰⁷, c) serotonin/norepinephrine re-uptake inhibitors (SNRI) to facilitate endogenous antinociceptive signaling⁴³, and d) minocycline to attenuate pronociceptive microglial activation⁶⁹.

Clinical Data on CDT for Chronic Pain

The concept of CDT for pain treatment was tested initially using fixed-dose drug combinations (e.g., acetaminophen with hydrocodone or oxycodone) and later in the perioperative setting with intrathecally or epidurally administered agents (e.g., clonidine with lidocaine³⁶ or morphine²). These neuraxial approaches were subsequently extended to patients with intractable pain from spinal cord injury using similar drug combinations delivered through indwelling intrathecal catheters⁹¹. By and large, the efficacy of CDT for chronic pain treatment remains unclear due to 1) a paucity of clinical studies that directly

compare single drug therapy with CDT and 2) the lack of standards used to conduct and analyze clinical studies of CDT⁷². As listed in Table 1, clinical studies on CDT fall into three general categories: 1) those comparing single- versus multi-drug therapy; 2) those evaluating “add-on” therapies (adding additional medications to an existing treatment regimen); and 3) those using translational research approaches examining preclinical findings in human subjects.

Single- versus multi-drug therapy

In such studies, the efficacy of a CDT was compared with that of a corresponding single drug therapy, some of which also explicitly included a placebo control group (Table 1). To date, there is well-documented evidence that combining agents acting at the $\alpha 2\delta 1$ subunit of voltage-gated calcium channel (gabapentin or pregabalin) with nortriptyline³² or opioid analgesic (morphine or oxycodone)^{30, 33, 40} provides better pain relief than the corresponding single drug therapy in patients suffering from painful diabetic neuropathy (PDN) or postherpetic neuropathy (PHN).

Other examples of effective CDT include such combinations as a) tramadol and acetaminophen⁹, tenoxicam and bromazepam⁷⁹, or fluoxetine and amitriptyline^{37, 109} for pain associated with fibromyalgia, b) tizanidine and amitriptyline for chronic tension-type headache¹⁰, and c) gabapentin and amitriptyline for chronic pelvic pain⁹⁰. However, a combination of ibuprofen and alprazolam did not result in better pain relief for fibromyalgia⁸⁶, nor did a combination of morphine and nortriptyline for lumbar radicular pain⁵¹ or of diclofenac and codeine or imipramine for cancer-related pain⁷⁰.

Add-on therapy

This type of CDT refers to drug therapies in which a selected medication is added to an existing treatment regimen (Table 1). This type of clinical study is frequently used to circumvent the usually problematic necessity of requiring pain subjects to discontinue their ongoing pain medications^{15, 64}. The benefit of add-on therapies (achieving better pain relief and/or maintaining functional recovery) has been demonstrated in a number of clinical studies, most notably by adding gabapentin or pregabalin to a preexisting drug therapy for pain from PDN and PHN^{24, 83, 88}, both of which obtained the approval by the US Food and Drug Administration (FDA) for clinical use as a single agent. Other examples of effective add-on therapies include adding into a preexisting, stable treatment regimen a) tramadol, acetaminophen, and/or NSAIDs^{56, 93, 104} for osteoarthritic pain; b) duloxetine⁸⁷ or pregabalin¹⁹ for fibromyalgia; and c) topical agents (capsaicin 8% vs. 0.04%) for PHN pain⁶.

However, a number of add-on therapies have failed to demonstrate a superior benefit with added drugs that include ketamine and amitriptyline⁶⁰, lamotrigine⁹², calcitonin and ketamine²⁶, or capsaicin and doxepin (both topical agents)⁶⁶ for neuropathic pain treatment. Importantly, it should be pointed out that while suggestive, studies using add-on therapies do not necessarily confirm a true therapeutic superiority of CDT, or lack thereof, because the study design does not explicitly include an arm of corresponding single drug therapy as a critical control.

Translational research

Despite promising preclinical findings, many potential drug combinations have failed to produce benefit in the treatment of an array of clinical pain conditions^{26, 50, 51, 70, 81, 94, 95, 99–101}. For instance, combinations of an N-methyl-D-aspartate (NMDA) or cholecystokinin (CCK) receptor antagonist with opioid analgesics were assessed in several large scale clinical trials because preclinical studies indicate that NMDA and CCK receptors were critically involved in the mechanisms of neuropathic pain and/or opioid tolerance^{62, 108}. In

both cases, combination therapies using the NMDA receptor antagonist ketamine or dextromethorphan^{28,29,49,53, 68} or the CCK receptor antagonist L-365,260⁶⁷ failed to produce either an increase in analgesic efficacy or a reduction in side effects. Several factors (e.g., inadequate preclinical pain model and assessment tools) may have contributed to the failure of these translational studies in the pain field^{15, 64, 72}, discussion of which is beyond the scope of this article.

Recent CDT studies in acute pain management

Recent studies on acute postoperative pain management have shown that while gabapentin decreased postoperative opioid use and improved functional recovery after total knee replacement¹⁷, gabapentin as an add-on therapy did not result in better pain relief, less opioid use, or better functional recovery following total hip arthroplasty¹⁶, nor did a combination of gabapentin and meloxicam enhance pain relief following laparoscopic cholecystectomy³⁴. These data suggest that the type of clinical condition may influence the effectiveness of CDT for acute postoperative pain treatment. At present, it is unclear whether disease conditions may also influence the clinical outcome of CDT in chronic pain management.

A Call for More Clinical Studies to Establish a Better Framework for CDT

To date, several consensus guidelines for single drug therapy in pain management have been reported^{25, 52}. By contrast, a limited number of clinical studies on CDT have been reported and their validity remains to be tested (Table. 1). An essential truth that is often lost in the management of complex cases is that adding more medications into a treatment regimen does not always lead to better pain relief and/or functional recovery, as noted in several failed clinical studies (Table 1), but surely increases the cost and possibly side effects of drug therapy³³. Importantly, other modalities of chronic pain management such as cognitive behavioral therapy, interventional procedures, physical therapy and rehabilitation should be considered in conjunction with drug therapy to achieve an optimal clinical outcome that includes gain of function^{58,73,98}. Given the widespread use of CDT in the absence of data demonstrating increased efficacy in drug combinations along with data highlighting potential deleterious consequences of CDT, it is essential that more clinical trials are initiated to provide the data necessary for the most effective utilization of this treatment strategy.

1: What are the therapeutic goals of CDT?

Prior to initiating a study on CDT, details of the particular patient population need to be considered. These must include the patient's overall clinical status, and medical and psychiatric comorbidities. Within the context of CDT, it is also essential to adequately assess the response to a single drug therapy^{5,7,35} as any meaningful interpretation of the efficacy of CDT has to occur within the context of the efficacy of a single drug therapy. Moreover, if single drug therapy appears to be ineffective, the underlying cause(s) for failure need to be determined including side effects. Furthermore, because of evidence indicating that CDT may not provide a better clinical outcome as compared to single drug therapy if pain relief is the only primary outcome measure, multiple outcome measures, including side effects and overall function must be monitored^{26,34, 51, 74, 81, 99–101, 109}.

2: How to choose drug combinations?

Clinical research needs to identify those factors that may influence the choice of drug combinations such as a) type of drug combinations based on the mechanisms of action, b) pain syndrome-specific targets, and c) adverse effects of drug combinations.

Type of drug combinations—Several types of drug combination are currently available: a) combination of drugs from the same drug class that differ in their pharmacokinetics (i.e., onset and duration of action), such as a combination of immediate with extended release opioid analgesics^{66, 103}; b) combination of two or more drugs from different drug classes, such as a combination of opioid with tricyclic antidepressant^{10, 25, 27, 48, 55, 57, 65, 71, 82, 103}; and c) combination of drugs delivered through different routes, such as a combination of topical agent (lidocaine or capsaicin) with oral agent (gabapentin)^{39, 76, 103}. Alternatively, fixed-ratio drug combinations are also widely used, which often consists of two drugs from different classes in a single dose formulation. For example, nearly all short-acting opioid analgesics are combined with either ibuprofen or acetaminophen (e.g., oxycodone/ibuprofen; tramadol/acetaminophen)^{77, 85, 97}.

Pain syndrome-specific drug combinations—As illustrated in figure 1, a variety of mechanisms contributes to chronic pain and its clinical comorbidities such as depression, which may be modulated with target-directed drugs. For example, chronic axial back pain without radicular symptoms and signs may benefit from non-opioid analgesics, whereas the treatment of neuropathic pain (e.g., PHN or complex regional pain syndrome type I) may include ion channel blockers, tricyclic antidepressants, SNRI, and/or topical agents¹⁰².

Adverse effects from drug combinations—Although reduction of side effects is a potential benefit of CDT, drug-related side effects could be augmented in CDT as well. In addition to common side effects of drug therapy such as nausea and light headedness, unique side effects from drug combinations (Fig 2) may include a) serotonin syndrome from a combination of tramadol and selective serotonin and/or norepinephrine reuptake inhibitor⁴⁴, b) worsening sedation and mental status change from tricyclic antidepressant and opioid analgesic, and c) liver toxicity from duloxetine and acetaminophen. It is critical to determine how CDT-related side effects may influence the choice of a drug combination in the clinical setting. For instance, sedation from a drug combination (e.g., antidepressant and opioid) will be a major concern for geriatric patients and patients who engage in public safety work (e.g., school bus driver) or operate heavy machinery; whereas tricyclic antidepressants may be less favored in patients with a known diagnosis of cardiac arrhythmia⁴.

3: How to evaluate CDT

Clinical studies are needed to determine the effectiveness of CDT using established clinical research approaches^{15, 64, 72, 84}. When possible, the gold-standard isobolographic analysis may be considered to examine the clinical synergistic vs. additive drug-drug interaction¹¹. An important issue to consider is whether the impact of CDT on pain relief and functional recovery is sustainable over time¹³. For instance, while adding opioid analgesic into an existing drug therapy may produce a short-term benefit, opioid-related side effects (e.g., constipation, hormonal change, opioid-induced hyperalgesia) may diminish the therapeutic benefit over time^{8, 63}. On the hand, the benefit of CDT may become apparent only after a long-term treatment such as using a combination of gabapentin and amitriptyline for chronic pelvic pain⁹⁰.

The influence of drug-drug interactions on the outcome of CDT is another important clinical issue¹⁰⁵. For example, the sedative effect of methadone and diazepam can be exacerbated because both are metabolized through the same cytochrome P450 system^{47, 14}. As with many other side effects, the impact of drug-drug interactions is a particular concern in geriatric patients because of age-related pharmacokinetic and metabolic changes^{4, 14, 42}. Combining even a small dose of opioid analgesic and tricyclic antidepressant may be enough to cause clinically significant constipation in geriatric patients with already diminished gastrointestinal motility¹⁰⁵.

In summary, CDT is a modality of drug therapy that has been widely used in clinical practice by both general practitioners and specialists. While CDT has been shown to be beneficial for certain chronic pain conditions, considerably more data is needed to provide guidelines for both the most appropriate choice of drug combinations and the most appropriate clinical setting for CDT. This article calls for more clinical studies to fully understand the mechanisms and clinical application of CDT in chronic pain management.

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Figure 1. Multiple mechanisms underlying chronic pain serve as targets for pharmacotherapy including CDT

A. While specific mechanisms may vary in association with an array of biological and social factors, several fundamental processes may serve as particularly good targets for available drugs. These processes include (1) transduction, which involves the conversion of thermal, mechanical and/or chemical stimuli in the local environment into a neural signal (action potential), (2) transmission of the neural signal in both peripheral and central axons, which is essential for the propagation of nociceptive signal from sites of injury or disease to cortical structures necessary for the perception of pain, (3) neuroplastic changes such as ectopic activity at the DRG (3a), synaptic transmission (3b), and descending modulation (3c) such as endogenous inhibitory processes that involves neural processes arising from brainstem nuclei that impact nociceptive input at the level of the spinal cord and trigeminal dorsal horn and can be facilitated with a number of drugs currently available. The final steps underlying the perception of pain (4) involve a number of cortical structures important for the sensory, emotional and cognitive aspects of pain. **B.** Currently available drugs can be used to attenuate pain via actions at all potential targets where the efficacy of specific classes of drug is likely to be determined by the relative involvement of a particular target in a particular pain phenotype. NSAID: non-steroidal anti-inflammatory drug; TCA: tricyclic antidepressant; SNRI: selective serotonin and norepinephrine re-uptake inhibitor; COX-2: cyclooxygenase-2; TNF α : tumor necrosis factor α .

Figure 2. A list of possible side effects with CDT

Examples of adverse effects from various drug combinations are shown in individual boxes. Common side effects such as nausea and dizziness could be exacerbated in any drug combination.

Table 1

Representative Studies of CDT for Chronic Pain

Pain Condition	Drug Combination	Study Type	Study Outcome	Reference
Spinal cord injury	Morphine, clonidine, or combination [intrathecal]	Single- vs. multi-drug comparison	Positive: Better pain relief with combination	91
Post-herpetic neuralgia, painful diabetic neuropathy	Morphine, gabapentin,, combination, or placebo [oral]	Single- vs. multi-drug comparison	Positive: Better pain relief with combination; a few more adverse events with combination	33
Painful diabetic neuropathy	Oxycodone, gabapentin, combination, or placebo [oral]	Single- vs. multi-drug comparison	Positive: Better pain relief and fewer adverse events with combination	40
Mixed neuropathic pain	Oxycodone, pregabalin, or combination [oral]	Single- vs. multi-drug comparison	Positive: Better pain relief and fewer adverse events with combination	30
Post-herpetic neuralgia, painful diabetic neuropathy	Nortriptyline, gabapentin, or combination [oral]	Single- vs. multi-drug comparison	Positive: Better pain relief and less frequent side effect (dry mouth) with combination	32
Lumbar radiculopathy	Morphine, nortriptyline, combination, or placebo [oral]	Single- vs. multi-drug comparison	Negative: No better pain relief with combination	51
Fibromyalgia	Tenoxicam, bromazepam, or combination [oral]	Single- vs. multi-drug comparison	Positive: Better pain relief with combination	79
Fibromyalgia	Fluoxetine, amitriptyline, or combination [oral]	Single- vs. multi-drug comparison	Positive: Better pain relief with combination	37, 109
Fibromyalgia	Ibuprofen, alprazolam, or combination [oral]	Single- vs. multi-drug comparison	Negative: No better pain relief with combination	86
Post-herpetic neuralgia	Gabapentin or placebo [oral]	Add-on	Positive: Better pain relief with add-on drug	83
Post-herpetic neuralgia	Pregabalin or placebo [oral]	Add-on	Positive: Better pain relief with add-on drug	24
Post-herpetic neuralgia	Pregabalin or placebo [oral]	Add-on	Positive: Better pain relief with add-on drug	88
Post-herpetic neuralgia	Capsaicin 8% or 0.04% [topical]	Add-on	Positive: Better pain relief with 8% than 0.04% capsaicin	6
Mixed neuropathic pain	Capsaicin (0.025%), doxepin (3.3%), or placebo [topical]	Add-on	Negative: No better pain relief with add-on drug	66
Mixed neuropathic pain	Amitriptyline 2%, ketamine 1%, or placebo [topical]	Add-on	Negative: No better pain relief with add-on drug	60
Phantom limb pain	Calcitonin, ketamine, or placebo [intravenous]	Add-on	Negative: No better pain relief with add-on drug	26
Fibromyalgia	Duloxetine, or placebo [oral]	Add-on	Positive: Better pain relief with add-on drug	87
Fibromyalgia	Pregabalin or placebo [oral]	Add-on	Positive: Better pain relief with add-on drug	19
Osteoarthritis	Tramadol+NSAIDs [oral]	Add-on	Positive: Better pain relief with add-on drug	104
Osteoarthritis	Tramadol+acetaminophen [oral]	Add-on	Positive: Better pain relief with add-on drug	56, 93