Combination pharmacotherapy for management of chronic pain: from bench to bedside

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Lancet Neurol 2013; 12: 1084–95

Published Online
September 25, 2013
http://dx.doi.org/10.1016/S1474-4422(13)70193-5

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Chronic pain, a frequently neglected problem, is treated with different classes of drugs. Current agents are limited by incomplete efficacy and dose-limiting side-effects. Knowledge of pain processing implicates multiple concurrent mechanisms of nociceptive transmission and modulation. Thus, synergistic interactions of drug combinations might provide superior analgesia and fewer side-effects than monotherapy by targeting of multiple mechanisms. Several trials in neuropathic pain, fibromyalgia, arthritis, and other disorders have assessed various two-drug combinations containing antidepressants, anticonvulsants, non-steroidal anti-inflammatories, opioids, and other agents. In some trials, combined treatment showed superiority over monotherapy, but in others improved benefit or tolerability was not seen. Escalating efforts to develop novel analgesics that surpass the efficacy of current treatments have not yet been successful; therefore, combination therapy remains an important beneficial strategy. Methodological improvements in future translational research efforts are needed to maximise the potential of combination pharmacotherapy for pain.

Introduction

Chronic pain is a common but often neglected aspect of neurological disease.[1] In the USA alone, it affects about 30% of the population and is estimated to cost US$650 billion a year in health-care costs and lost productivity.[2] Pharmacotherapy remains an important component of multimodal, multidisciplinary pain management. However, current drugs have limited efficacy and dose-limiting toxic effects.[3] Although translational research efforts to develop more effective treatments have led to some novel agents, we have yet to address the clinical need fully.[4] While awaiting better agents, and to address these limitations of current pharmacotherapy, combination drug regimens have been pursued by researchers and clinicians with the intention of improving outcomes.[5,6] Combination pharmacotherapy is used commonly for treatment of acute postoperative pain, and its use has a wide evidence base. Rational combination therapy has long been used in clinical areas such as asthma,[7] oncology,[8] and hypertension,[9] but only more recently for pain management. Although more than half of patients with chronic pain receive two or more different analgesic drugs concurrently,[10] relatively little evidence supports this practice, and experts have called for more research on the safety and efficacy of specific combination regimens.[3,11]

Through knowledge of pain processing, many concurrent mechanisms of nociceptive transmission and modulation can be targeted.[12] Thus, synergistic interactions between mechanistically distinct analgesic drugs might provide superior analgesia or fewer side-effects compared with monotherapy.[13,14] In this Review, we discuss preclinical literature, clinical data, and other information addressing the rationale, practice, and future directions of combination pharmacotherapy for pain. We do not review combination treatment for headache, which is discussed elsewhere.[15]

Pain mechanisms and clinical classification

Nociceptive processing represents an important alarm system to warn of tissue damage.[12,16,17] Pain is signalled by specialised high-threshold receptors in the periphery, leading to a less well-defined emotional experience, driving the individual to escape from the noxious stimulus.[18] Acute nociceptive pain occurs only in the presence of noxious stimuli and resolves shortly after removal of the stimulus. Chronic pain, however, seems to serve no purpose. It is a state in which increased activity is present in the nociceptive signalling system because of either sustained input in peripheral sensory nerves or abnormal activity in those parts of the nervous system that modulate sensory information. This abnormal modulation can lead to either increased facilitation in central zones or insufficient inhibition in pain-transmitting and pain-modulating circuits.[12,19,20] Chronic pain is typically divided into three major classes: inflammatory (eg, arthritis), neuropathic (eg, postherpetic neuralgia), and idiopathic (eg, fibromyalgia). These classifications are adapted mainly from preclinical evidence from which distinct and separable mechanisms have been identified from neuropathic and inflammatory models, and there are various different diseases and causes; in the case of neuropathic pain, these can be categorised according to the assumed underlying pathology and the anatomical location of the disorder (table 1).

Inflammatory pain is a response to tissue injury and is accompanied by neurogenic inflammation.[12,21,22] It results from the release of sensitising inflammatory substances (eg, prostanoids, bradykinin) that reduce the activation threshold of the nociceptors innervating the inflamed tissue, increasing the response to activation and yielding abnormal responses in the CNS to sensory inputs as a result of increased neuronal excitability. These events, although evoked within minutes, can outlast the tissue injury for hours to days. Tissue changes after inflammation are reversible if healing occurs, and the sensitivity of the system is restored after inflammation has resolved. In chronic inflammatory conditions, nociceptive signalling pathways are intact and in a state of heightened sensitivity to ensure optimum healing. Signs of

inflammation—such as swelling, redness, and increased temperature—are usually present. As a result, pain in the inflamed body area partly promotes avoidance from contact or movement and, thus, protection from further damage.

Neuropathic pain follows injury or disease affecting peripheral nerves or sensory pathways within the spinal cord or brain.[23] Neuronal lesions result in sensory loss in the territory corresponding to damaged nerves or to the peripheral projections of CNS structures. Therefore, an important distinction from inflammatory pain is that neuropathic pain can sometimes be combined paradoxically with sensory loss in the painful area.[24]

Idiopathic pain, or pain of unknown origin, refers to a group of disorders (eg, fibromyalgia, chronic whiplash) in which the underlying mechanisms are poorly understood. The general absence of inflammation, nerve injury, major psychiatric illness, or other documentable pathological features is such that these conditions represent diagnoses of exclusion. A feature of idiopathic pain is a local or generalised increase in sensitivity to noxious and non-noxious stimuli.[19,20,25] Idiopathic pain has also been termed functional or dysfunctional pain. These terms should be avoided because they carry the connotation that these symptoms might represent malingering (the conscious simulation of painful symptoms), which is a very rare condition[26] and clearly different from idiopathic pain.

These pain subcategories are somewhat artificial and do not respect individual variations. Patients can present with diverse pain complaints not necessarily accounted for by a purely inflammatory or neuropathic cause, and in many cases a chronic pain condition might represent a mixture of these different subcategories. For example, in osteoarthritic pain such as lower back pain, which is normally classified as an inflammatory type of pain, additional neuropathic (eg, an irritant effect on afferent nerve fibres from inflamed tissue) and even neuroplastic (eg, sustained peripheral activity causing central sensitisation) components can be present.

A characteristic of most pain conditions, irrespective of cause, is a set of common signs that include elicitation of pain by low threshold input, spread of pain outside the injured territory, pain that outlasts stimulation, and an augmentation of pain with repetitive stimuli (temporal summation). These common events are attributable to sensitisation within the CNS, which is defined as amplification of neuronal activity within the CNS that gives rise to hypersensitivity in sensory processing, including increased pain sensitivity.[20] Although central sensitisation is activity-dependent and driven from the periphery, it can also become self-sustained once developed and enhanced or recruited by central mechanisms, such as loss of inhibition in central descending pathways[27] or increased activity in noxious facilitating systems within the CNS.[28,29]

	Peripheral	Spinal	Brain
Genetic	Fabry neuropathy	Syringomyelia	Syringobulbia
Metabolic	Painful diabetic neuropathy	B12 myelopathy	..
Traumatic	Nerve injury	Spinal cord injury	..
Vascular	Vasculitic neuropathy	Spinal cord stroke	Stroke
Neoplastic	Tumour compression neuropathy	Tumour compression	Tumour compression
Immunological	Guillain-Barré syndrome	Multiple sclerosis	Multiple sclerosis
Infectious	HIV, borreliosis	Infectious myelitis	Encephalitis
Toxic	Chemotherapy neuropathy	..	..

Characteristic examples are provided within every category.

***Table 1*: Classification of neuropathic pain according to site of injury and type of pathology**

Pain diagnosis and identification of underlying pathological processes require clinical examination,[19] which can be facilitated by different available questionnaires that, with reasonable sensitivity and specificity, can distinguish between neuropathic and non-neuropathic pain. These questionnaires include the Leeds assessment of neuropathic symptoms and signs (LANNS) scale, painDETECT, ID-Pain, and douleur neuropathique 4 (DN4).[30] However, they do not identify specific pathological features or causes and, for that reason, a clinical examination is mandatory. In addition to clinical assessment, a careful sensory examination should be done to elicit the hypoaesthetic and hyperaesthetic abnormalities that characterise neuropathic pain.

Pharmacological treatment

A major goal of pain management is to provide pain relief that is clinically meaningful, sustained, and associated with minimum and reversible adverse effects.[11] Defining what is a clinically meaningful reduction in pain is challenging, and only a few studies have attempted to do so. Secondary analyses from a group of industry-sponsored chronic pain trials suggest that a 30% pain reduction is clinically meaningful.[31] In some settings, a lower level of relief can be meaningful if there are few adverse effects. Because chronic pain is sometimes associated with mood disturbance, anxiety, and sleep interference,[32] pain treatments that concurrently improve these other symptoms are preferred. However, some CNS-depressant effects might impair a patient's mobility and ability to exercise, which are crucial for successful rehabilitation in several pain conditions.

Table 2 lists recent consensus recommendations for pharmacological treatment of chronic non-malignant pain.[11,33–35] Chronic pain is generally characterised by heightened sensitivity and increased response to noxious stimuli (hyperalgesia) and pain produced by normally non-noxious stimuli (allodynia).[19] This sensory hyperexcitability can often be suppressed by analgesics, including anticonvulsants, antidepressants, and

	First-line and second-line recommendations	Third-line and fourth-line recommendations	Not recommended
Neuropathic pain[31]	First-line: tricyclic antidepressants, SNRI antidepressants, anticonvulsants (gabapentin or pregabalin); second-line: tramadol, opioids	Bupropion, citalopram, paroxetine, carbamazepine, lamotrigine, oxcarbazepine, topiramate, valproic acid, dextromethorphan, memantine, and mexiletine	..
Osteoarthritis of the hip or knee[33]	Paracetamol, NSAIDs, tramadol	..	Chondroitin sulfate, glucosamine, opioids, duloxetine
Fibromyalgia[34]	Muscle relaxants, tricyclic antidepressants, SSRI and SNRI antidepressants, tramadol, anticonvulsants (gabapentin or pregabalin)	..	Opioids*
Low back pain[35]	Paracetamol, NSAIDs, COX2 inhibitors, muscle relaxants, tramadol	Opioids†, antidepressants, anticonvulsants	Benzodiazepines, systemic corticosteroids

We have summarised recommendations from consensus statements from the last decade. COX2=cyclo-oxygenase-2. NSAIDs=non-steroidal anti-inflammatory drugs. SNRI=serotonin–noradrenaline reuptake inhibitor. SSRI=selective serotonin reuptake inhibitor. *Third-line recommendation by only one of three consensus statements. †Reported as potentially harmful by some consensus statements

Table 2: **Systemic pharmacological treatments recommended for management of chronic non-malignant pain**

opioids.[36] These antihyperalgesic drugs exert their effects respectively on Ca^{2+} channels, Na^{+} channels, monoamine uptake mechanisms, and G-protein-coupled membrane receptors expressed in neurons that are widespread throughout the nervous system in peripheral, spinal, brainstem, limbic, and cortical structures. As such, CNS depressants also potentially cause sedation, dizziness, and memory problems, whereas combinations of drugs with additive analgesic effects but not cumulative adverse effects represent a possibility to lower the dose of single agents and thereby reduce side-effects.

Combination pharmacotherapy

Efficacy of single agents for chronic pain is limited, with less than a third of patients reporting at least moderate pain relief. So, there is a need either to develop new and more effective drugs or to identify favourable combinations of drugs that are already available. Several concurrent neural mechanisms of pain modulation have a role in clinical syndromes, providing a strong rationale for combination pharmacotherapy. While addressing the limitations of current treatments, intense translational research efforts have led to an explosion of knowledge about novel pain mechanisms and pharmacological targets.[12] However, as with other areas of neurotherapeutics, this work has not yet provided a solution to control pain, although some improved pain treatments have been developed.[4] In clinical practice, the observation of partial benefit with one analgesic can lead prescribers to pursue polypharmacy in an add-on fashion.[37] In fact, recent reports indicate that more than half of patients with chronic pain receive two or more different analgesic drugs concurrently.[10] The findings of some studies show that specific combinations provide no additional benefit or, worse yet, increase adverse effects. In lumbar radiculopathy, monotherapy with either nortriptyline or morphine failed to show efficacy, and the combination of the two drugs provided no added benefit.[38] In phantom limb pain, ketamine—but not calcitonin—showed efficacy, but their combination was no better than ketamine alone.[39] Finally, in post-herpetic neuralgia, combining the phenothiazine agent fluphenazine with amitriptyline provided no added analgesia compared with amitriptyline alone, although sedation was increased.[40] These and other examples emphasise the need for expanded research on combination pharmacotherapy, both from mechanistic and empirical perspectives, to identify beneficial combinations and to guide selection of combinations in a rational manner. Broadly speaking, addition of a second drug to an effective but suboptimum first drug could have several effects. First, better pain reduction could occur by addition of a second analgesic, either through complementary actions or actions that in some other way potentiate the efficacy of the first drug. Second, an improved side-effect profile might be noted either with a second drug that directly antagonises the adverse effects of the first drug (eg, an opioid plus a CNS stimulant) or with a combination that provides maximum analgesia at such low doses that overall side-effects are reduced. Finally, expanded improvement of other related symptoms (eg, sleep disturbance, depression, anxiety) might be seen—eg, night-time addition of a sedating antidepressant drug to a non-steroidal anti-inflammatory (NSAID). Another rationale for combination therapy is to target the different pain mechanisms that coexist within an individual—eg, a patient with inflammatory and neuropathic causes of low back pain could benefit from both an anti-inflammatory and an antineuropathic treatment.

Pain modulation and mechanistic rationale for combination therapy

Advanced preclinical research methods facilitate investigation of mechanisms underlying neuropathic and inflammatory pain, thereby enabling development

of more effective treatments. The peripheral mechanisms of these two pain subtypes are very different and treatments vary, yet signalling systems within the CNS seem to be common. In idiopathic pain disorders, such as fibromyalgia, the underlying mechanisms of pain are more likely to be central, although recent evidence also points to possible peripheral mechanisms in some patients.[41]

Within a pain syndrome, many mechanisms are clearly in operation at peripheral and central sites (figure 1). The pivotal issue lies in identification of the pain-modulating role of signalling molecules in the context of the whole animal and then translating this knowledge to the patient. The net balance of activity within the nervous system establishes the final sensation. Thus, in-vivo models (ie, integrated systems)

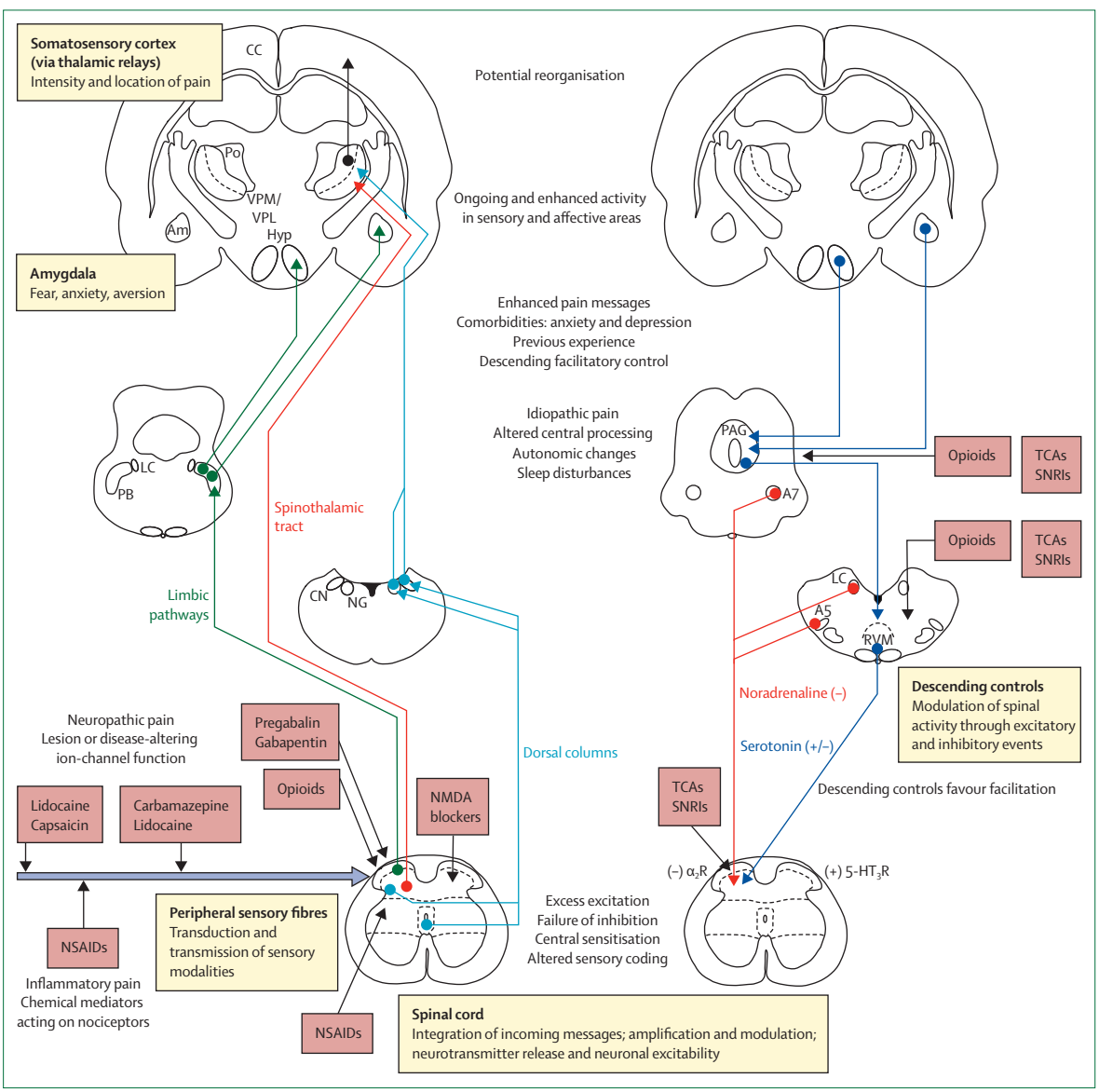

Figure 1: **Main pathways and mechanisms by which pain is transmitted and modulated**
The ascending pathways, by which sensory and affective components are generated, are shown on the left. Top-down modulation, by which higher centres can alter spinal function through changes in descending controls, is shown on the right. The major functional roles of the different neural components in these pathways are summarised in yellow boxes. Changes that occur after tissue or nerve damage are listed, and pharmacological agents that modulate pain are shown at their sites of action in red boxes. Peripheral inputs are indicated by the horizonal purple arrow. The peripheral mechanisms of inflammatory and neuropathic pain are very different, and this difference is reflected in their different treatments. However, central mechanisms might be more common than peripheral mechanisms. (–) α_2R=inhibition of neuronal activity. (+) 5-HT_3R=stimulation of neuronal activity. Am=amygdala. A5 and A7=brainstem nuclei containing noradrenergic neurons. CC=cerebral cortex. CN=cuneate nucleus. Hyp=hypothalamus. LC=locus coeruleus. NG=nucleus gracilis. NSAIDs=non-steroidal anti-inflammatory drugs. PAG=periaqueductal grey matter. PB=parabrachial nucleus. Po=posterior nuclei of the thalamus. RVM=rostro-ventral medial medulla. SNRIs=serotonin–noradrenaline reuptake inhibitors. TCAs=tricyclic antidepressants. VPM and VPL=ventrobasal thalamus, medial and lateral components.

are essential to study pain because the interactions between peripheral activity, spinal transmission and modulatory systems, and interactions with brain systems determine net overall activity that leads to the sensation of pain.[12] In preclinical studies, drug mechanisms can be investigated at peripheral and central sites with pharmacological, anatomical, and molecular genetic techniques; increasingly, the results of this work are linking well with clinical science.[4]

Preclinical studies of analgesic drug interactions

What are the underlying mechanisms of pain? Peripheral nociceptors are activated continually when tissue is damaged (figure 1). Production of chemical mediators in and around the damaged area leads to peripheral sensitisation, such as that produced by prostanoids, which is the basis for use of NSAIDs to treat pain with inflammatory causes. Targeting of cytokines and growth factors that have a role in these processes has led to some new agents for pain control.[4] By contrast, changes in ion channels, particularly Na^+ channels, as a result of a lesion or disease are thought to cause abnormal peripheral neuropathic pain. Translation of some of these mechanisms comes from human familial pain disorders, validating the idea that abnormal firing of Na^+ channels results in pain.[42,43] Clinical use of Na^+ channel blockers such as lidocaine or carbamazepine lends further support to this idea. Evoked and spontaneous pain might turn out to have different mechanisms and, indeed, within familial pain disorders of Na^+ channels, the ability of carbamazepine and mexiletine to induce pain relief vary even though the same channel is targeted.[44] This difference is probably attributable to the state of the channel block by the different drugs (eg, open, closed, inactive)[45] but suggests that teasing out mechanism-based treatments might be even harder than envisaged.

Nerve trauma causes abnormal impulse propagation towards the spinal cord and striking changes in Ca^{2+} channels (increased numbers of channels and subunits, and functional roles), which lead to release of more neurotransmitter (eg, glutamate and substance P), favouring spinal hypersensitivity. Indeed, pronounced upregulation of Ca^{2+} channel subunits happens at spinal levels, corresponding to innervation of the damaged nerve.[46] Now, in the spinal cord, enhanced release of glutamate and substance P leads to activation of receptors (eg, the NMDA receptor), which generates an increase in the intensity of pain (wind up) and central sensitisation, both of which are plausible mechanisms for chronic pain states[20,47] in which neurons reduce their thresholds and expand their receptive fields, leading to continual firing. It is here that ketamine exerts its analgesic actions by modulation of NMDA receptor-driven activity. After peripheral inflammation, similar mechanisms at spinal levels are initiated by peripheral chemical sensitisation, leading to an increased drive from the damaged tissue. Many drugs work on the principle of restoring balance between excitation and inhibition of chronic pain, by either increasing inhibition (eg, with opioids) or decreasing excitatory input (eg, with gabapentin) to restore the physiological status of gates in the spinal cord, brainstem, and higher centres.[29] The actions of some drugs depend on the state of CNS pain pathways; therefore, they target pathophysiological rather than physiological pain. For example, gabapentin and pregabalin bind to the α2δ subunits of voltage-gated Ca^{2+} channels and disrupt trafficking of this channel to the synaptic membrane and ultimately restrict Ca^{2+} entry into the neuron, reducing neurotransmitter release.[46] Crucially, this process occurs in hyperexcitable neurons in which turnover and trafficking of voltage-gated Ca^{2+} channels is high. Furthermore, because nerve injury is associated with preferential presynaptic upregulation of these subunits in the ipsilateral dorsal horn, inhibition by gabapentin (or pregabalin) is regionally selective and correlates temporally and spatially with the nerve injury. Opioids can exert some of their actions at the spinal cord, where the combination of presynaptic and postsynaptic inhibition reduces transmitter release and neuronal activity. After nerve injury, presynaptic receptors produced in the dorsal root ganglion might be vulnerable to the lesion or disease of the nerve and, thus, opioid dosing might need to be higher compared with inflammatory pain.[48]

Antidepressants that inhibit reuptake of serotonin and noradrenaline—eg, duloxetine—might be useful as an adjuvant treatment when the benefits of gabapentin plateau. Potential synergy between these agents indicates important links between brainstem areas (particularly those drugs that affect serotonin and noradrenaline release) and treatment efficacy.[49,50] Indeed, preclinical data show that drugs acting on monoamine systems interact within a spinal cord–brain–spinal cord loop that includes brain centres important in emotional and aversive responses to pain. These brain centres will be activated not only by pain, which shifts the balance from noradrenergic inhibition towards serotonergic facilitation, but also by so-called top-down processes such as fear, anxiety, and other life events that start to dominate in chronic pain states. These pathways then descend to facilitate spinal mechanisms of pain, showing the key interplay between sensory and psychological events in pain processing.[51] Changes in these systems explain the efficacy of gabapentin or pregabalin alongside the alterations in spinal voltage-gated Ca^{2+} channels,[52] but they can be also modulated by opioids. Thus, the action of opioids not only is confined to spinal presynaptic and postsynaptic inhibition but also can switch descending controls in the brainstem to inhibition by interaction with neurons at the origin of the descending controls.[28,48]

In this respect, several drugs can target peripheral, spinal, and supraspinal sites to suppress aberrant

transmitter or channel function in different pain states. These actions provide a rationale for combination treatment in view of the multiple sites and mechanisms operant in pain states such as neuropathy. A major guiding principle here is to combine agents that act via different mechanisms or sites of action, since two targets can be attacked at once. In theory, increasing activity in inhibitory systems while decreasing excitatory transmission might be preferable. Combining drugs with peripheral and central sites of action might block transmission at the site of neuropathy and modulate its central outcomes. Thus, peripherally administered lidocaine for a focal neuropathy could be combined with a centrally acting agent (eg, opioid, anticonvulsant, or antidepressant). However, the timing of administration must account for the pharmacokinetic variables of combined agents so that maximum effectiveness of both agents overlaps temporally. Animal neuropathy experiments show that gabapentin plus morphine, opioids plus ketamine, and other combinations in which excitation is blocked concurrently with enhancement of inhibition results in increased antinociception.[53] For example, low doses of gabapentin plus morphine, which alone have little effect, produce substantial antinociception when used in combination.[54,55]

Formal demonstration of synergy requires complex and resource-intensive isobolographic analyses (ie, analyses of graphs plotting different doses of two drugs to produce constant efficacy, alone and in combination); however, in many cases, supra-additive effects are clear with less extensive analyses. The drug tapentadol has been shown to produce synergistic μ opioid activation and noradrenaline reuptake inhibition in animal models. In combination with pregabalin there is again synergism with tapentadol, but only additive effects with some side-effects are seen when pregabalin is combined with pure opioids.[56] It would be interesting to test the clinical consequences of these pharmacological interactions.

Optimising clinical outcomes of combination pharmacotherapy

Maximising clinical effectiveness of combination pharmacotherapy requires careful attention, to balance beneficial and adverse interactions between the coadministered treatments. The panel highlights key considerations for selection of an optimum combination in chronic pain. In view of the efficacy and tolerability limitations of current treatments, the most intuitive guiding principle would be to combine the drugs with the maximum safety and efficacy. Also, a fundamental understanding of potential pharmacokinetic and pharmacodynamic interactions between the combined drugs is important.[57]

Safety considerations

A foremost safety consideration is avoidance of adverse drug interactions.[58] For example, findings of case reports and in-vitro studies suggest that the combination of serotonin reuptake inhibitors (eg, antidepressant drugs such as amitriptyline, desipramine, or duloxetine) with other analgesic drugs that also block serotonin reuptake (eg, tramadol) might increase the risk of developing serotonin syndrome, a potentially life-threatening adverse drug reaction associated with changes in mental status, autonomic hyperactivity, and neuromuscular dysfunction.[59,60] Another important safety concern is electrocardiographic QT prolongation, which has been reported with tricyclic antidepressants, serotonin–noradrenaline reuptake inhibitor antidepressants, and methadone. Combining drugs with these effects can increase the risk of torsades de pointes—a lethal cardiac arrhythmia.[60] Another potential interaction[60] is augmented risk of gastrointestinal bleeding when NSAIDs are coadministered with antidepressants (eg, amitriptyline, venlafaxine).

Optimisation of the therapeutic profile

The optimum combination of two effective analgesic drugs that have complementary analgesic actions and substantially different side-effect profiles is associated with little overlap of side-effects, such that the side-effect profile is minimised and efficacy is maximised. For example, in a meta-analysis of postoperative pain, NSAIDs resulted in diminished pain, sedation, and nausea or vomiting when combined with opioids, which is probably attributable to analgesia-related reductions in patient-administered opioid doses.[61] However, several conditions—such as neuropathic pain—respond predominantly to drugs that cause CNS-depressant effects (eg, antidepressants, anticonvulsants,

***Panel:* Considerations for selecting an optimum combination therapy in chronic pain**

Ideally, combine treatments with:

- maximum efficacy, fewest toxic effects, and minimum adverse interactions with other commonly used drugs
- minimum adverse drug interactions with one another
- different (non-overlapping) side-effect profiles*
- different pharmacological actions†
- different site of action†

These are general considerations to be applied to a generic combination therapy. However, other unique considerations might arise for specific combinations and specific pain conditions.

*Although optimum combinations include treatments with differing side-effect profiles (eg, NSAID and opioid), most available effective treatments for some disorders (such as neuropathic pain) have similar side-effect profiles (eg, CNS depression) and, despite this, some of these treatments have still been shown to provide added benefit in combination. †From a mechanistic viewpoint, combining treatments with different pharmacological mechanisms and sites of action could be expected to provide maximum synergy. However, examples have been described whereby treatments with common mechanisms and sites of action can provide added benefit.

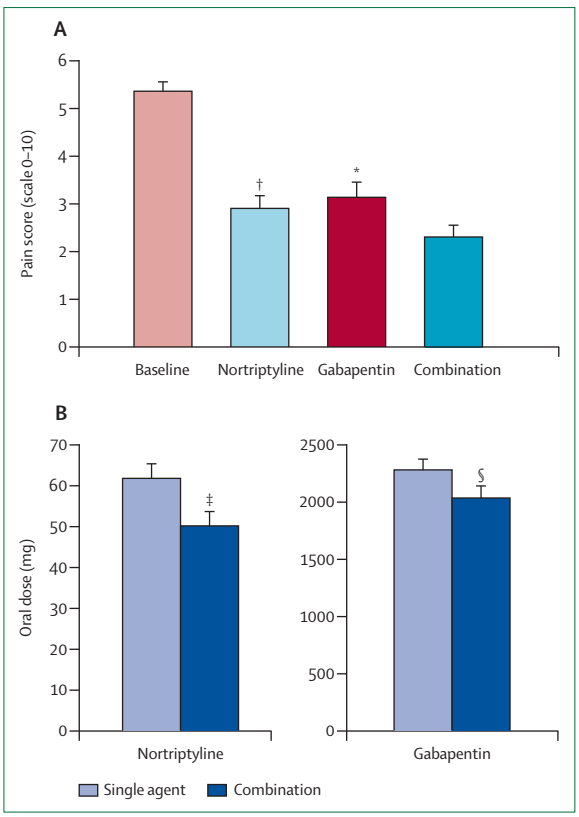

Figure 2: **Pain measurements and maximum drug doses in a study comparing gabapentin, nortriptyline, and their combination in patients with neuropathic pain**

(A) Mean daily pain scores (measured on a numerical rating scale of 0–10) at the maximum tolerated dose for each drug are shown (errors bars show 95% CI). Pain with combination treatment was significantly lower than with gabapentin (–0·9, 95% CI –1·4 to –0·3; p=0·001)* or nortriptyline (–0·6,–1·1 to –0·1; p=0·02)† alone. (B) Mean maximum tolerated doses of the single agent versus the combination (errors bars show SE). Differences between nortriptyline or gabapentin as monotherapy, and the combination, were significant (‡p=0·0006; §p=0·0009). Adapted from Gilron et al,[62] with permission of Elsevier Science.

and opioids).[11] Therefore, the benefits gained from combinations of such CNS depressants might be more difficult to appreciate in view of the possibility that adverse effects could also be additive. However, recent evidence suggests that some two-drug combinations of analgesics, both CNS depressants, can indeed provide an overall benefit.[5]

In a randomised trial comparing maximum tolerated doses of gabapentin, morphine, and a gabapentin–morphine combination for neuropathic pain,[62] CNS side-effects (eg, sedation) common both to gabapentin and morphine and expected to be additive were not more frequent during combination therapy, possibly because the individualised and flexible dose-titration was stopped when disabling side-effects arose. Although the frequency of CNS side-effects did not differ, unsurprisingly, maximum tolerated drug doses were significantly lower during combination treatment versus either monotherapy—probably attributable to some overlap of CNS side-effects. However, even at lower maximum tolerated doses, pain intensity was significantly diminished during combination versus either monotherapy.[62]

In a subsequent, similarly designed randomised trial,[63] a nortriptyline–gabapentin combination was compared with either drug as monotherapy in neuropathic pain. Similar to the previous trial, the frequency of CNS side-effects did not differ between groups, yet maximum tolerated doses of nortriptyline and gabapentin were significantly lower during combination treatment. In addition to lower pain intensity (figure 2), these findings showed that sleep interference was significantly reduced during combination treatment versus either monotherapy.[63]

Considering that overlapping CNS side-effects might explain lower maximum tolerated drug doses during combination treatment, it is somewhat puzzling that—even at lower drug doses—pain intensity was decreased during combination therapy yet frequencies of CNS side-effects were not higher. One hypothesis to account for the discrepancy between additive analgesia versus additive side-effects in both these trials[62,63] is that the analgesic mechanisms of gabapentin, morphine, and nortriptyline all act at peripheral, spinal, and supraspinal sites, whereas the sedative sites of action of these drugs are predominantly supraspinal. Thus, even if the two treatments being combined are CNS depressants, a superior therapeutic profile can be attained with such combinations.

In a large (n=804), multicentre double-blind trial,[64] an oral pregabalin (300 mg/day) and duloxetine (60 mg/day) combination was compared with either high-dose monotherapy (600 mg/day pregabalin or 120 mg/day duloxetine) in patients with painful diabetic neuropathy who failed to respond to monotherapy at lower doses (300 mg/day pregabalin or 60 mg/day duloxetine). The primary analysis was negative (ie, no significant difference between combination and high-dose monotherapy for the primary pain outcome); however, all secondary outcome measures favoured combination treatment, and side-effects were generally similar in both groups.[64] However, in animal models, descending facilitations can be prerequisite for the actions of pregabalin;[49] therefore, the probable interaction of duloxetine with these descending systems might compromise the actions of pregabalin. Other more recent combination trials are ongoing or completed[5] and are awaiting publication.

Current status of combination pharmacotherapy

The findings of recent studies into treatment patterns for various pain conditions[10,65,66] suggest that about half of patients with chronic pain receive two or more different analgesic drugs concurrently. Commonly prescribed drug combinations include fixed-dose formulations of paracetamol combined either with

opioids (eg, codeine) or tramadol, NSAIDs plus opioids, muscle relaxants plus opioids, antidepressants plus anticonvulsants, antidepressants plus opioids, and anticonvulsants plus opioids. However, the evidence base supporting such combinations is limited.

In a 2012 Cochrane review of combination pharmacotherapy for neuropathic pain,[5] 21 randomised controlled trials were identified. Combinations of an opioid with gabapentin or pregabalin were assessed in four trials (n=578 patients); combinations of fluphenazine with a tricyclic antidepressant were investigated in three trials (n=90); opioids combined with a tricyclic antidepressant were evaluated in two trials (n=77); gabapentin and nortriptyline was studied in one trial (n=56); and various other combinations were assessed in 11 other trials. The conclusion was that many good-quality studies show superior efficacy of some two-drug combinations versus monotherapy, but the number of available studies for a specific combination currently preclude recommendations for neuropathic pain. Since most combinations investigated included drugs causing CNS depression, the overall benefits of such combinations could be limited. Therefore, the anticipated development of peripherally acting and non-sedating drugs for neuropathic pain could provide more favourable combinations in which side-effects are not compounded. Several methodological challenges have been highlighted (table 3) that could guide future improvements for trials of combination pharmacotherapy. In particular, fewer than half the studies in the Cochrane review compared a double-drug combination to each monotherapy. The problem with such an incomplete study design is that any differences between a combination of drugs (A+B) versus only one drug alone (eg, A) could be attributable strictly to differences in efficacy between drugs A and B and, thus, additional comparison of A+B with B alone is necessary for comprehensive evaluation of the combination.

23 studies were compared in a 2011 Cochrane review of combination pharmacotherapy for inflammatory arthritides.[80] Combinations of an NSAID with an antipyretic analgesic (paracetamol or benorilate) were compared with an NSAID alone in 12 studies; combinations of two different coadministered NSAIDs were compared with one NSAID alone in five studies; and various other combinations were assessed in six other studies. The randomised trials included in the review, which were all published before 1994, were identified to be at high risk of bias, leading to the conclusion of insufficient evidence to support combination therapy for inflammatory arthritis.[80] However, most studies compared two-drug

	Combination studied	Trial comparisons			
		Placebo-controlled	Combination *vs* only one component	Combination *vs* both components	Combination *vs* other treatment
Agrawal et al (2009)[67]	Oral valproate + topical glyceryl trinitrate	Yes	..	Yes	..
Amr (2010)[68]	Intravenous ketamine + oral gabapentin	..	Yes	..	..
Caraceni et al (2004)[69]	Oral opioid + oral gabapentin	..	Yes	..	..
Eichenberger et al (2008)[39]	Intravenous calcitonin + intravenous ketamine	Yes	..	Yes	..
Freeman et al (2007)[70]	Oral paracetamol + oral tramadol	Yes	..	..	Yes
Gilron et al (2005)[62]	Oral gabapentin + oral morphine	Yes	..	Yes	..
Gilron et al (2009)[63]	Oral nortriptyline + oral gabapentin	..	..	Yes	..
Gomez-Perez et al (1985)[71]	Oral nortriptyline + oral fluphenazine	Yes	..	..	Yes
Gomez-Perez et al (1996)[72]	Oral nortriptyline + oral fluphenazine	..	..	..	Yes
Graff-Radford et al (2000)[40]	Oral amitriptyline + oral fluphenazine	Yes	..	Yes	..
Hanna et al (2008)[37]	Oral oxycodone + oral gabapentin	..	Yes	..	..
Khoromi et al (2007)[38]	Oral nortriptyline + oral morphine	Yes	..	Yes	..
Lynch et al (2003)[73]	Topical amitriptyline + topical ketamine	Yes	..	Yes	..
Lynch et al (2005)[74]	Topical amitriptyline + topical ketamine	Yes	..	Yes	..
McCleane (2000)[75]	Topical doxepin + topical capsaicin	Yes	..	Yes	..
McCleane (2003)[76]	Oral morphine + oral L-365,260 (cholecystokinin blocker)	..	Yes	..	..
Mercadante et al (2002)[77]	Oral morphine + oral amitriptyline	..	Yes	..	..
Tonet et al (2008)[78]	Oral ketamine + oral amitriptyline + oral carbamazepine	..	Variant*	..	..
Zin et al (2010)[79]	Oral oxycodone + oral pregabalin	..	Yes	..	..

Adapted from Chaparro et al,[5] with permission of the Cochrane Collaboration. *Comparison of amitriptyline + carbamazepine + ketamine *vs* amitriptyline + carbamazepine; all other studies listed assessed only two-drug combinations.

Table 3: **Methodology of combination therapy trials in neuropathic pain**

combinations to only one of the monotherapies, leaving in question the relative contribution of the other agent.

Limited evidence supports combination treatment for other painful conditions, as emphasised by the scarcity of published randomised trials in this area. No systematic reviews and fewer than half a dozen trials of combination pharmacotherapy have been reported in osteoarthritis, including paracetamol plus NSAID.[81] Other fixed-dose combination formulations (eg, paracetamol–opioid or paracetamol–tramadol) have not been compared with the respective components. This lack of evidence is reflected in the 2012 American College of Rheumatology treatment recommendations for hip and knee osteoarthritis, suggesting that patients "should use one of the following"[33]: paracetamol, NSAIDs, or tramadol.

It is noteworthy that in a recent systematic review of chronic low back pain[82] (possibly the most common chronic pain condition), only four double-blind studies were eligible for review, and two of these compared a fixed-dose tramadol–paracetamol combination with placebo only. Further to the few trials identified, another difficulty is that studies of lumbar radiculopathy were mixed with those of largely non-neuropathic back pain. In addition to the trial of a morphine–nortriptyline combination,[38] findings of another study (n=36) suggested that the combination of pregabalin plus celecoxib was superior to either drug alone.[83] Finally, in a systematic review of trials evaluating the combination of one opioid with a different opioid in cancer pain,[84] only one double-blind randomised trial (n=26) was identified, suggesting that a combination of morphine–oxycodone was superior to morphine alone. However, the combination was not compared with oxycodone alone.[85]

Clinical approaches to combination pharmacotherapy

Clinically speaking, a distinction should be made between different methods of introducing a two-drug combination—ie, whether the two drugs are administered simultaneously at the outset or whether the second agent is introduced sequentially (in an add-on fashion).[86] In view of the need to improve patients' safety by minimising polypharmacy,[87] a guiding principle is to first assess the response to one drug (drug A). If drug A is well tolerated and efficacious, this monotherapy could be continued and regularly reassessed. If drug A either produces intolerable adverse effects or inadequate relief, it should be abandoned, with consideration for switching to another treatment (drug B). If, however, drug A is well tolerated with only partial pain relief, then consideration could be given to continuation of drug A and initiation of drug B in an add-on fashion. When drugs A and B are both CNS depressants (eg, antidepressants, anticonvulsants, or opioids), the dose of drug A is typically titrated to the patient's maximum tolerated dose, to make the most of pain relief. In this situation, the dose of drug A is generally near the limits of tolerability and the amount of add-on dose titration of drug B could be limited if the side-effects of drug A are further compounded by addition of drug B. Therefore, sequential combination treatment might not allow titration of sufficiently effective doses of drug B because of overlapping side-effects. If instead both drugs A and B are started simultaneously at low doses and similarly titrated to the maximum tolerated dose, this approach might allow for a more balanced dose ratio. Thus, the application of trial data to clinical practice should be done in the context of how the drugs were combined in the relevant trial—ie, simultaneously versus sequentially.

Conclusions and future directions

Combination pharmacotherapy for treatment of pain conditions, including those seen in neurological disorders, remains an important—and understudied—strategy. Future improvements in the development of combination strategies will be guided by enhanced preclinical strategies to predict optimum combinations, including methods to assess the interactions of multiple concurrent analgesic drugs and adverse effects relevant to patients' care. As emphasised in this Review and elsewhere,[88] trials must evaluate the components of the combination with each of the constituent drugs on their own, to best show the value added by the combination. In view of the need to understand pharmacokinetic and pharmacodynamic interactions between components of an analgesic combination, careful attention is needed to define the optimum dose ratio between components, although this requirement might complicate design of clinical studies further. For CNS depressant drugs that need gradual dose titration towards a maximum tolerated dose, a sequential method of add-on combination treatment will probably result in an unbalanced ratio that includes preferentially high doses of the first drug titrated; alternatively, simultaneous combination might result in a more evenly balanced dose ratio. Finally, analgesic combinations are not a research priority for the pharmaceutical industry, possibly due to the high cost and complexity of combination trials but potentially also because of the head-to-head element of combination trial designs, whereby proprietary single agents compete with one another. Therefore, creative solutions must be advanced to encourage drug developers and other research funding agencies to support this important aspect of pain management research.

The widespread use of polypharmacy in pain management reflects current limitations of available pharmacotherapies as single agents and, more importantly, emphasises the need for combination-specific research to distinguish between beneficial and

Search strategy and selection criteria

We searched Medline between January, 1946, and March, 2013, with the following keywords: "pain*" OR "analgesi*" OR "nocicepti*" OR "antinocicepti*" OR "neuralgia" OR "fibromyalgia" OR "sciatica"; AND "combin*" OR "cotreat*" OR "co-treat*" OR "coadminist*" OR "co-administ*" OR "synerg*" OR "isobol*" OR "add on*" OR "add-on*". From the results, we identified preclinical investigations, randomised controlled trials, other observational studies of interventions, and reviews. We also searched by hand for articles in reference lists of relevant reviews and clinical trial registries. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the scope of this Review.

useless or even harmful drug combinations. Available evidence showing that some, but not all, combinations are superior to their single-agent components suggests that continued research in this area has the potential to improve clinical outcomes. Carefully integrated bench-to-bedside combination research programmes, with input from academia, industry, and government regulators, is expected to identify new treatment strategies that are badly needed to improve the management of pain.

Contributors

All authors contributed equally to the development, literature search, and writing of the Review and have all approved submission of the final version.

Conflicts of interest

IG has received support from Pfizer, Aventis Pharma, Novopharm, PharmaScience, Apotex, Merck-Frosst, Johnson & Johnson, Ortho-McNeill, and Janssen-Ortho; and has received grants from the Canadian Institutes of Health Research, Physicians' Services Incorporated Foundation, and Queen's University. AHD has received speakers fees from Astellas, Bristol-Myers Squibb, Grunenthal, and Pfizer; and has received support from Grunenthal. TSJ has received support from Astellas, Grunenthal, and Pfizer.

Acknowledgments

Our work has been supported in part by a Canadian Institutes of Health Research (CIHR grant number MSH-55041) award to IG. IG is part of the Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks (ACTTION) partnership. AHD is part of the Wellcome Trust-funded London pain consortium. TSJ and AHD are part of the EU-IMI consortium, EUROPain. We thank Shafaq Sikandar for assistance with this Review.

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