

PHARMACOTHERAPY

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“Levels of Evidence” used in this section:

Level 1: Meta-analysis or systematic reviews.

Level 2: One or more well-powered randomized, controlled trials.

Level 3: Retrospective studies, open label trials, pilot studies.

Level 4: Anecdotes, case reports, clinical experience, etc.

INTRODUCTION

For the past 150 years, multiple pharmacotherapeutic interventions for complex regional pain syndrome (CRPS) have been described — ever since Mitchell discussed laudanum (tincture of opium) and the use of a new invention, the hypodermic syringe, to perform cocaine nerve blocks.¹⁻⁴ However, even today, unfortunately, few medications for CRPS have been tested in double-blind, randomized controlled trials (RCTs).⁵ The best clinical approach must therefore employ the sparse data available, extrapolate from better evidence that is available in related conditions (particularly neuropathic pain),⁶ and ultimately utilize empirical drug trials in each specific case, based on putative mechanisms.³ CRPS comprises both nociceptive/inflammatory and neuropathic elements and is always (by definition) associated with abnormal activity of the sympathetic nervous system.⁷ According to reliable data, CRPS is now hypothesized to variably include central sensitization,⁸ motor abnormalities,⁹ and sympathetic efferent features⁸ at different times and in different individuals.^{7,10} Because the syndrome presents in numerous forms and most likely evolves over time, a universal pathophysiology or a common natural history have not been identified.^{7,10} Given the many variables involved in CRPS diagnoses, the current taxonomy and diagnostic criteria give a reasonably functional definition of CRPS (see section one). Although this is a significant improvement over the diagnostic disarray of the past, current taxonomy and diagnostic criteria still fall far short of the ideal (see section one). The absence of a gold-standard diagnostic test or a specific mechanistically based diagnostic scheme has impeded the ability to conduct well-designed trials, and, to date, scant evidence exists to indicate effective treatment for often desperate patients.

For the resourceful clinician, RCTs of specific drug treatments and systematic reviews of treatments for related neuropathic conditions can yield useful information when extrapolated to clinical use in CRPS. Pharmacotherapy with some evidence of efficacy for CRPS include tricyclic antidepressants, gabapentin, carbamazepine, opioids, clonidine, nifedipine, calcitonin, bisphosphonates, α -adrenergic antagonists, the 5% lidocaine patch, and topical capsaicin. This section reviews the available data on pharmacotherapeutic options for CRPS, as well as those pertinent drug therapies that can be extrapolated from the neuropathy literature.

Pharmacotherapy, as with most chronic pain syndromes, achieves the greatest results when it is prescribed in conjunction with functional restoration and an interdisciplinary approach to treatment (see section two).

Although monotherapy is preferred when possible, “rational polypharmacy” in the treatment of CRPS is frequently required to optimize analgesia. In order to effectively apply rational polypharmacy, the clinician must formulate a reasonable hypothesis for the underlying pain mechanism(s) and match a rational combination of drugs that interfere with that (those) mechanism(s) at different sites in the neuroaxis. The clinician must construct a rational prescription that draws from two basic classes of medications: prophylactic drugs (maintenance, drugs used on a scheduled basis) to manage pain and other symptoms, and abortive drugs or “rescue agents” (used as needed; “PRN”) for breakthrough pain or symptom flares. The most rational approach to rescue agents is to follow the World Health Organization (WHO) treatment ladder: begin with simple analgesics, evolve as needed to more potent (and more controversial) opioids, and finally proceed to drug combinations.¹¹ Additionally, the prophylactic drug(s) prescribed will usually be chosen according to the patient’s other symptoms. For example, if a CRPS patient is extremely depressed and/or anxious and has insomnia, the clinician may select a heterocyclic antidepressant with significant analgesic, sedative and anxiolytic properties.

Medications, particularly rescue medications, are primarily intended to provide patients with the relief necessary to allow them to engage in other interdisciplinary modalities. It is these other modalities, including physical therapy, occupational therapy, and recreational therapy, that are most likely to provide extensive and enduring improvement, and the most likely to affect the pathophysiology of the disorder per se. Although analgesia for its own sake has obvious value, that value is short-termed. Long term goals should be taken into account whenever a pharmacotherapeutic regimen is developed.¹²

ANTI-INFLAMMATORY DRUGS/IMMUNOMODULATORS

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), corticosteroids, Cox-2 inhibitors, and free-radical scavengers are generally used to treat pain and the inflammatory symptoms of CRPS. Some researchers hypothesize that the inflammatory components are critical to the development or perpetuation of CRPS.^{13, 14} These medications can be used for both rescue, and in the case of long-acting agents, as prophylactics. Although the WHO ladder recommends their early use,¹¹ both patients and practitioners alike often succumb to the “nocebo” bias (ie, the belief that certain drugs are “too simple” to be effective against something as complicated as CRPS). If this preconception can be overcome, NSAIDs can be quite effective, in our clinical experience (level 4 evidence). In addition to treating CRPS, NSAIDs have also been used to treat other neuropathic pain conditions, particularly those associated with considerable inflammation (level 3 evidence).¹⁵⁻¹⁸

NSAIDs inhibit cyclooxygenase and prevent the synthesis of prostaglandins, which mediate inflammation and hyperalgesia. In addition to their peripheral anti-inflammatory action, NSAIDs may also block spinal nociceptive processing.^{17, 18} NSAIDs, however, have shown mixed results in several clinical trials of neuropathic pain, including one trial that showed that NSAIDs had no value in treating CRPS I.¹⁹ Certain NSAID drugs may be more effective than others. Ketoprofen, for example, has substantial antibradykinin and antiprostacyclin effects as well as the typical antiprostaglandin effect. Even though inhibitors selective for cyclooxygenase-2 (eg, celecoxib, rofecoxib) have not been tested in CRPS, they have been reported anecdotally to be of some use (level 4 evidence).²⁰

Oral corticosteroids are the only anti-inflammatory drugs with strong evidence of benefit in CRPS (level 1 evidence).¹⁵ Similar results were observed in the treatment of poststroke shoulder-hand syndrome, which is often indistinguishable from and diagnosed as CRPS I. Steroids may demonstrate differential efficacy in the early/acute phases of CRPS, especially when significant inflammation is present. Two prospective RCTs^{21,22} using a pulse of oral corticosteroids (approximately 30 mg/day for 2-12 weeks, followed by a tapering period) in patients with early acute CRPS yielded notable improvements when compared with placebo (mean of 12 weeks' duration; level 2 evidence). It should be noted, however, that a later systematic review of the literature²³ evaluated one of these trials²¹ and considered it to be of low quality. Given the data, a short course of steroids may be indicated, but longer courses have a questionable risk benefit ratio,¹⁵ and there are numerous, obvious contraindications to chronic steroid use.

Reactive oxygen species are known to have a role in inflammatory processes that may be involved in CRPS I. Free radical scavengers (eg, dimethyl sulfoxide; DMSO and vitamin C) may reduce the concentration of these compounds. A double-blind, placebo-controlled study of the antioxidant vitamin C was found to reduce the incidence of "RSD" in patients with wrist fractures²⁴ (see below under topicals for DMSO).

In neuropathic pain, neuroimmune interactions may occur and provide the rationale for immunosuppressive/immunomodulatory therapy. Animal studies^{25,26} with cyclosporine, thalidomide, and methotrexate support this premise. Thalidomide (TNF- α and IL-1 and -6 inhibitor, among other immunomodulatory actions) has shown some promise, first in case reports²⁷ and later in open label trials.^{28,29} A specific TNF- α was reported as helpful in a case report.³⁰ The next generation of immunomodulatory compounds (these are also referred to as IMiDs) such as lenalidomide are showing some promise in open label trials^{31,32} and RCTs are in progress. Etanercept and infliximab have been anecdotally mentioned.³³

ANTICONVULSANTS/NEUROMODULATORS

There are meta-analytic and systematic reviews providing substantial evidence for the efficacy of certain anticonvulsant compounds as prophylactic agents in neuropathic pain (level 1 evidence).³⁴⁻³⁷ Anticonvulsants work by a variety of mechanisms thought to be relevant in CRPS. Some block sodium and calcium channels, producing a decrease in neuronal excitability³⁸; some work centrally on GABA, NMDA, "non-NMDA" and presynaptic mechanisms.³⁴⁻³⁷ Some of them show significant promise in the treatment of CRPS and are frequently used clinically (level 4 evidence in CRPS). In fact gabapentin, widely used for neuropathic pain, first came to the attention of the research community when an anecdotal report touted its effect in the treatment of CRPS (referred to as reflex sympathetic dystrophy in that publication).³⁹ Although of theoretical interest to practitioners dealing with CRPS, the mechanism of action of gabapentin is not completely understood.⁴⁰ It was originally hypothesized to enhance endogenous gamma-aminobutyric acid (GABA) systems that help modulate pain (but it is not a GABA agonist); it may play a role in suppressing excitatory amino acids such as glutamate and Ca⁺ transmission⁴¹; and it also may have a significant effect on presynaptic vesicle formation/function.⁴²

Large RCTs of gabapentin have proven its efficacy in postherpetic neuralgia and diabetic peripheral neuropathy (level 2 evidence).^{43,44} A case series in adult patients⁴⁵ and a case report in a pediatric patient⁴⁶ suggest its efficacy in CRPS (level 4 evidence). The efficacy of specific GABA-ergic/agonist drugs in CRPS drugs has not been adequately studied. Phenytoin and other “membrane stabilizing” antiepileptic drugs (Na⁺ channel blockers) may aid in treating CRPS, especially in cases involving nerve damage (Type II) or in cases involving heightened ectopic activity as a potential pain generator (level 2 evidence).⁴⁷⁻⁴⁹ RCTs for lamotrigine have studied its effects on other neuropathic conditions, but not CRPS.⁵⁰

Carbamazepine is membrane stabilizing as well as tricyclic and has a traditional and perhaps clinically important place in the treatment of CRPS.^{51,52} One RCT⁵³ of patients with CRPS indicates that 600 mg/day of carbamazepine, taken over 8 days, yields considerable pain reductions when compared to placebo (level 2 evidence). The results of an open-label trial⁵⁴ (level 3 evidence) in patients with painful diabetic neuropathy indicate that oxcarbazepine may provide efficacy equal to carbamazepine, while providing fewer side effects. It should be noted that oxcarbazepine has not been studied specifically in CRPS. There is anecdotal evidence for a variety of other anticonvulsants/neuro-modulators, but no compelling research at this time. In our clinics, levitiracetam and topiramate seem to be useful in some cases.

ANTIDEPRESSANTS/ANXIOLYTICS

A traditional choice in neuropathic conditions (level 2 evidence),⁵⁵⁻⁵⁸ heterocyclic antidepressants (HCAs) are used exclusively as maintenance agents. Meta-analyses^{34,35,57} of RCTs support HCA efficacy for neuropathic pain. One study⁵⁷ reported that, for every 100 patients with neuropathic pain taking antidepressants, 30 would obtain at least 50% pain relief (Number Needed to Treat [NNT] of 3).⁵⁹ The antihyperalgesic effects of HCAs may be linked to mechanisms that are independent of their antidepressant effects (eg, enhancement of noradrenergic descending inhibitory pathways and peripheral sodium-channel blockade).⁶⁰

When pain is independent of a stimulus (spontaneous, as opposed to evoked), it is reasonable to target mechanisms causing sensitization of primary somatosensory afferents. HCAs act centrally by inhibiting the reuptake of both serotonin and noradrenaline; those that have more serotonin activity (eg, doxepin, imipramine) may be more effective for painful polyneuropathy compared to those with relative selectivity for noradrenaline reuptake (eg, desipramine), based on a lower NNT for one patient to achieve at least 50% pain relief (NNT= 2.0 vs. 3.4).^{34,61} There is some evidence supporting the use of HCAs in CRPS (mostly level 4 evidence).¹⁵ In an open-label study⁶² of 41 children with CRPS, two patients obtained complete pain relief, 21 patients obtained substantial relief, and 18 patients obtained poor relief (level 3 evidence).

The good clinician must possess a repertoire of several tricyclic/quadracyclic drugs, because each drug possesses specific side effects, and these may sometimes be used to the patients' advantage.^{58,63} For example, an anxious, depressed, thin, insomniac patient may benefit from a sedative, anxiolytic, antidepressant (eg, doxepin); conversely, a patient who is depressed, overweight, and hypersomnolent with psychomotor retardation may benefit from a tricyclic antidepressant with more noradrenergic selectivity (eg, desipramine), which may be activating and can cause some anorexia.⁵⁶

Selective serotonin reuptake inhibitors (SSRIs) have not shown analgesic efficacy (level 4 evidence).^{64, 65} The NNT for SSRIs in neuropathic pain is much higher than traditional HCAs: 7.7 for citalopram vs. 2.9 for paroxetine.³⁴ Certain newer antidepressant agents such as mirtazepine and the Selective Norepinephrine and Serotonin Reuptake inhibitors (SNRI) such as venlafaxine have shown some anecdotal value in our clinics (level 4). They also possess different and relatively benign side effect and toxicity profiles, but there is essentially no evidence in CRPS. The newer SNRIs (ie, milnacipran, duloxetine, bupropion) may hold some promise, but this theory must be tested.

OPIOIDS

The use of opioids for general chronic pain management is still subject to some controversy,^{15, 66} but they may have value as both a rescue and a maintenance treatment for CRPS. In an early validation of their efficacy, Mitchell¹ commented that “for the easing of neurotraumatic pain...the morphia salts... are invaluable.” Only one RCT has been conducted⁵³ evaluating the use of controlled-release morphine in CRPS, and that trial reported no difference in pain reduction when compared to placebo after a short course of 8 days’ use. Although only this single RCT of opioids in CRPS exists, many studies⁶⁶⁻⁶⁸ of opioids for neuropathic pain do indicate their efficacy (level 2 evidence).

In general, neuropathic pain does not respond to opioids as well as nociceptive pain does⁶⁹⁻⁷¹; consequently, neuropathic pain requires higher doses, but this also increases the risk of side effects. Obviously, long acting agents should be used for maintenance prophylaxis and as a short-acting agent for rescue. Methadone may have a special place in the treatment of CRPS because of its putative NMDA antagonism,⁷² and weak-opioid tramadol may be helpful due to its concomitant serotonin/norepinephrine re-uptake block. Tolerance and long-term toxicity are unresolved issues for the moment,^{66, 73} and some animal data has raised a theoretical concern that long-term opioid use may actually elicit allodynia and/or hyperpathia.⁷⁴

Mitchell also comments on tolerance: “When continuously used, it is very curious that its hypnotic manifestations lessen, while its power to abolish pain continues, so that the patient who receives a half grain or more of morphia may become free from pain, and yet walk about with little or no desire to sleep,”¹ and human tolerance is a complex phenomena, that clearly is not linear, as in the animal models. However, it must be noted that tolerance to the analgesic effects of opioids in humans has not yet been shown to be a significant clinical issue in controlled prospective studies.

Opioids are clearly not a panacea, since there are many unresolved concerns about tolerance, cognitive impairment (especially with “rescue dosing”), and opioid induced hyperalgesia. Thus, it behooves the astute clinician to not become overenthusiastic about this class, but to keep them in the proper place in the armamentarium. Optimum care in our opinion entails the use of nondrug therapies preferentially, nonopioid medications for maintenance, and the use of opioids in crisis management.³ The use of opioid therapy should be linked to increased participation in the functional restoration process, as with all drugs or interventions.

NMDA RECEPTOR ANTAGONISTS

For several decades, NMDA receptor antagonists (eg, MK-801, ketamine, amantadine, and dextromethorphan) have been taken into consideration for the treatment of neuropathic pain and for CRPS specifically, but their toxicity (intolerable side effects, as well as potential CNS damage) at effective dose levels have proven too high for regular human use in oral formulations.⁷⁵⁻⁷⁹ Ketamine has shown favorable results in one small RCT of cancer patients with neuropathic pain unresponsive to morphine (level 2 evidence),⁸⁰ and in case reports⁸¹⁻⁸³ of patients with CRPS (level 4 evidence). Considerable ongoing interest exists regarding high dose inpatient protocols, and lower dose in- or outpatient protocols; a variety of delivery systems are also the subject of study.⁸⁴ Amantadine has shown some benefit in cancer patients with neuropathic pain (level 2 evidence)⁸⁵ and in patients with chronic neuropathic pain (level 4 evidence).⁸⁶ Plain dextromethorphan in pill form may be better tolerated and may augment the effect of other medications, especially opioids.⁸⁷

ANTI-HYPERTENSIVES AND α -ADRENERGIC ANTAGONISTS

Clonidine is an α -adrenergic agonist that has been considered for the treatment of CRPS.⁸⁸ It has been suggested to have benefit epidurally in “sympathetically maintained pain” (see ⁸⁹; level 3) A case series⁹⁰ showed that transdermal clonidine could reduce or eliminate local CRPS-induced hyperalgesia and allodynia (level 4 evidence). According to a recent systematic review,¹⁵ available data regarding clonidine is unconvincing overall (level 1 evidence). Nifedipine, a calcium channel blocker, has demonstrated efficacy for the management of symptoms sometimes associated with CRPS (eg, for control of intense vasoconstriction; level 4 evidence). Two uncontrolled case series^{91,92} indicated that doses of nifedipine of up to 60 mg/day were useful for the treatment of CRPS.⁹¹

Phenoxybenzamine and phentolamine are nonselective α -adrenergic antagonists that some clinicians have suggested for CRPS therapy. Two case series^{91,93} (level 4 evidence) support the efficacy of oral phenoxybenzamine, which seems to have an optimal effect in syndromes of less than 3 months’ duration.⁹¹ Because parenteral phentolamine is expensive, only available in limited supply, and usually administered by continuous intravenous infusion, it is not widely used clinically. As a diagnostic tool for distinguishing sympathetically maintained pain, however, phentolamine may provide a more specific diagnosis, because of a lower rate of false-positive results, compared to local anesthetic blockade of sympathetic ganglia.^{94,95}

CALCITONIN

Interestingly enough, calcitonin is one of the best-studied drugs in the treatment of CRPS.⁹⁶⁻⁹⁹ A polypeptide hormone, calcitonin provides some analgesic effects and it regulates both bone metabolism and blood calcium levels.⁹⁸ A meta-analysis¹⁰⁰ of a limited number of controlled studies (level 1 evidence) demonstrates the value of intranasal doses of 100-300 U per day for the management of CRPS.^{98, 100, 101} Two other clinical trials^{96,98} of calcitonin in CRPS, however, which were both identified as high-quality studies (level 2 evidence) in a systematic review, reported conflicting results.²³ One study reported significant improvement in pain intensity after administration of 100 IU calcitonin thrice daily for 3 weeks.⁹⁸ The other study reported no improvement after administration of 200 IU calcitonin twice daily for 4 weeks.⁹⁶

BISPHOSPHONATES

Bisphosphonates (eg. alendronate, clodronate, pamidronate) hinder bone resorption and may be useful in the treatment of CRPS. They are probably the best studied, and perhaps the most promising class of drugs to date. A systematic review of the literature²³ identified two high-quality studies of bisphosphonates for the treatment of CRPS^{102, 103} (level 2 evidence): one study evaluated intravenous administration of clodronate (300 mg daily for 10 days),¹⁰² and the other evaluated intravenous administration of alendronate (7.5 mg daily for 3 days).¹⁰³ Both studies reported significant improvement in reports of pain. There is a good quality, mid-sized RCT of oral alendronate suggesting efficacy in CRPS.¹⁰⁴ Since the systematic review, there have been two small RCTs of oral pamidronate that have suggested some benefit.^{105, 106} Additionally, there is a case series¹⁰⁶ (level 4 evidence) that also supports the efficacy of pamidronate for CRPS. The impact of these drugs on the osteopenia (Sudeck's atrophy) that is sometimes prominent in the disorder is unknown.¹⁰⁴

ADDITIONAL SYSTEMIC DRUG TREATMENT OPTIONS

Sildenafil augments the activity of nitric oxide and inhibits phosphodiesterase-5.¹⁰⁷ Some clinicians are currently experimenting with sildenafil to produce vasodilation in their patients with CRPS, but no reports have been published as yet. Some clinicians have experimented with the use of mexiletine, an orally administered antiarrhythmic drug with local anesthetic properties, for neuropathic pain, even though the results of one RCT¹⁰⁸ studying HIV-associated neuropathy were negative. We have encountered many problematic side effects with mexiletine. Systemic lidocaine, administered intravenously or subcutaneously, may be valuable in treating neuropathic pain.¹⁰⁹

TOPICAL TREATMENTS

Topical treatments for CRPS differ from transdermal medications like the fentanyl or clonidine patch because they only supply medication locally to the affected skin and soft tissue area. Topical treatments for CRPS include the 5% lidocaine patch, the Eutectic Mixture of Local Anesthetics (EMLA) cream, capsaicin and DiMethylSulfOxide (DMSO). There is some literature endorsing the use of EMLA for patients with CRPS¹¹⁰ (level 3 evidence), but RCTs have not been performed.

The lidocaine patch is a nonwoven patch containing 5% lidocaine; it is FDA-approved for the management of postherpetic neuralgia, and is used increasingly for CRPS.¹¹¹ It is critical to realize that this novel formulation of lidocaine does not produce any anesthesia but rather only analgesia, unlike most other topical local anesthetic formulations. An open-label study (level 3 evidence) showed improvement in five out of five patients.¹¹² The lidocaine patch may have efficacy in some very local or focal CRPS phenomena, such as allodynia.¹¹³ Capsaicin, a vanilloid compound found in chili peppers, causes activation and the dying-back of nociceptive nerve endings by allowing unchecked cation influx. Capsaicin frequently provokes a painful burning sensation at the site of application. In an RCT (level 2 evidence),¹¹⁴ topical capsaicin showed efficacy in treating postherpetic neuralgia. A preliminary study¹¹⁵ of patients with CRPS who were administered high-dose topical capsaicin using regional anesthesia demonstrated partial efficacy (level 3 evidence). We have found that topical capsaicin is intolerably painful, messy, and associated with very poor compliance.¹¹⁶⁻¹²⁰ DMSO is a free radical-scavenging agent. In a high quality study¹²¹ (level 2 evidence)

assessed in a systematic review,²³ DMSO (50% cream for two months) showed significant pain reduction when compared with placebo.

CONCLUSION

A methodical, patient approach to pharmacotherapy in CRPS is essential. To attempt to identify prominent mechanisms involved in the pain generation, and to try to match drug mechanisms of action to these is the *sine qua non* of the drug therapy of CRPS. It is often necessary to use more than one drug, or “rational polypharmacy”; and the goal is often as much to relieve the pain as to allow progress in interdisciplinary rehabilitation. This is theoretically the best hope for comprehensive management of the syndrome, as drug therapy alone is never enough.

In most cases, no single drug will provide sufficient analgesia long term, nor will it completely prevent the need for abortive/rescue agents. This clinical reality usually requires two or even multiple medications to adequately manage the pain. Thus, the problem of drug-drug interaction is critical to consider, but unfortunately the literature is very weak in this regard. The traditional sources of information, such as the *Physician's Desk Reference*[®], are somewhat helpful, but it is important to consider competitive metabolic or catabolic pathways, such as the liver cytochrome P450 catabolic systems. For instance, the 2D6 enzyme pathway catabolizes codeine, heterocyclic drugs, tramadol, mexilitine, and methadone (among others), and the prudent clinician would keep this in mind when combining these drugs. It is also important that if a drug-drug interaction is observed, this information should be reported and published.

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FIGURE 1. PHARMACOTHERAPY GUIDE. THE FOLLOWING STRATEGIES ARE SUGGESTED FOR PATIENTS WHO HAVE BEEN DIAGNOSED WITH CRPS BUT WHO CANNOT BEGIN OR PROGRESS IN THE FUNCTIONAL RESTORATION ALGORITHM *:

REASON FOR INABILITY TO BEGIN OR PROGRESS	ACTION
Mild-to-moderate pain	Simple analgesics and/or blocks (see section 5)
Excruciating, intractable pain [†]	Opioids and/or blocks or later, more experimental interventions (see section 5)
Inflammation/swelling and edema	Steroids, systemic or targeted (acutely) or NSAIDs (chronically); immunomodulators
Depression, anxiety, insomnia	Sedative, analgesic antidepressant/anxiolytics and/or psychotherapy (see section 3)
Significant allodynia/hyperalgesia	Anticonvulsants and/or other sodium channel blockers and/or NMDA-receptor antagonists
Significant osteopenia, immobility trophic changes	Calcitonin or bisphosphonates
Profound vasomotor disturbance	Calcium channel blockers, sympatholytics and/or blocks (section 5)

*It is important to remember that these suggestions are overruled by individual patient presentation.

[†]It is also important to note that certain drugs, such as bisphosphonates, may be associated with analgesia as well as the more primary action.