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The efficacy of current treatment options for Complex Regional Pain Syndrome

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THE EFFICACY OF CURRENT TREATMENT OPTIONS FOR

COMPLEX REGIONAL PAIN SYNDROME

by

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ABSTRACT

Complex Regional Pain Syndrome (CRSP) is a neuropathic disorder that has proven to be particularly difficult to treat based on the wide array of symptoms experienced by patients and the ambiguity surrounding their origin. The vast majority of treatment options today deal with the management of pain symptoms experienced by patients as a result of neuroinflammation. Physical therapy is an instrumental aspect of the treatment plan; however the need for more effective pharmacological interventions is paramount.

This study reviews a large volume of current and fundamental literature covering the plethora of treatment options currently used for CRPS. Data from double blind clinical trials as well as observational clinical results were gathered in hopes of illuminating the efficacy of each treatment. The goal was to assess current and future treatment options and determine what interventions are optimal for the management of CRPS.

Furthermore, this review highlights some of the limitations of the current treatment options, in addition to providing a synopsis of CRPS as it is understood today. This paper paints a picture of where we have been in the treatment of CRPS, what is working, what is not working, and where we might go in the future.

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ABBREVIATIONS

CNS	Central Nervous System
CRPS	Complex Regional Pain Syndrome
SRD	Sympathetic Reflex Dystrophy
SSRI	Selective Serotonin Reuptake Inhibitor
TCA	Tricyclic Antidepressant
TLR4	Toll-Like Receptor 4

INTRODUCTION

CRPS is a relatively new distinction that is used to describe a range of symptoms that are associated with neuropathic pain arising after trauma. CRPS is usually the result of a localized injury to an extremity with typical spreading and worsening of symptoms in the afflicted region (Birklein, 2005). The injury can and usually is minor in nature, often coming in the form of a trivial sprain or bone fracture. More severe injuries have been known to be associated with CRPS, such as peripheral nerve damage. A further classification of CRPS has been established to account for cases in which nerve damage is present. CRPS type 1 usually manifests after a trivial injury as mentioned above and does not include any nerve damage. CRPS type 2 results after direct peripheral nerve damage and is typically more severe than type 1.

CRPS has been known by many other names such as Reflex Sympathetic Dystrophy (RSD), Causalgia, and Sudek Atrophy. The origin and diagnostic criteria of the disorder have proven elusive to physicians. Under the RSD terminology, the pain associated with CRPS was believed to be associated with a reflex arc and thus a direct result of nerve damage (Rho et al., 2002). Recently however, this notion has lost favor as there are cases of CRPS that do not present with any nerve damage whatsoever. The confusion surrounding the syndrome was addressed by Dr. Norman Harden who proposed a set of criteria that is used to clinically diagnose CRPS (Harden, 2007). His consensus

determined that an irritating or noxious event triggers CRPS or results in a prolonged period of immobilization, which then leads to CRPS. Additionally, CRPS presents with continuing pain or hyperalgesia, which is an increased sensitivity to pain, disproportionately to the stimulus of said pain. The International Association for the Study of Pain finally established a diagnostic set of symptoms some or all of which may be present in patients suffering from CRPS (Table 1).

General definition of the syndrome:
CRPS describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time

To make the *clinical* diagnosis, the following criteria must be met:
1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in *three of the four* following categories:
   Sensory: Reports of hyperesthesia and/or allodynia
   Vasomotor: Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
   Sudomotor/Edema: Reports of edema and/or sweating changes and/or sweating asymmetry
   Motor/Trophic: Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign **at time of evaluation** in *two or more* of the following categories:
   Sensory: Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
   Vasomotor: Evidence of temperature asymmetry (>1°C) and/or skin color changes and/or asymmetry
   Sudomotor/Edema: Evidence of edema and/or sweating changes and/or sweating asymmetry
   Motor/Trophic: Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

Table 1: Criteria for the Clinical Diagnosis of CRPS. The complexity of the syndrome and the diverse symptoms has created a degree of ambiguity for clinical diagnosis (Rho et al, 2002).

The pain associated with CRPS is due to neuroinflammation with subsequent edema and hyperalgesia. CRPS typically has several symptoms and physical manifestations of neuroinflammation. Most often CRPS manifests following trauma to one of the limbs. Following the trauma, primary afferent neurons are activated by locally released cytokines, which results in further

release of neuropeptides both locally and in the Central Nervous System (CNS) (Birklein, 2005). The belief now is that it is the release of these neuropeptides that causes most of the symptoms of CRPS including the two most significant: pain and hyperalgesia (Birklein, 2005). Most often the limb is characterized by erythema, hyperalgesia, allodynia, decreased motor function, and edema. Patients have a difficult time performing simple daily tasks with the affected limb. CRPS is often accompanied by several psychological and psychosocial conditions including depression, anxiety, and reduced quality of life (Lohnberg and Altmaier, 2012).

Several non-surgical treatment options exist for CRPS including physical therapy, drug intervention, and sympathetic block (Rho et al., 2002). Physical therapy can be effective in restoring motor function; however the severe pain associated with movement makes physical therapy extremely difficult and taxing on the patient. As a result of the grueling physical therapy and prolonged period of pain, antidepressants are commonly administered to patients afflicted with CRPS. Pharmacological interventions such as gabapentin, antidepressants, and opioids together have been shown to manage pain in patients (Figure 1). Recently Forouzanfar et al. concluded that the use of sympathetic block is largely ineffective in reducing pain symptoms in patients with CRPS, but remains a viable treatment option for some patients (Forouzanfar, 2002). Additionally, new studies utilizing ketamine, naltrexone, and thalidomide have shown promise in curtailing the pain associated with CRPS.

| Medication | Usual oral dose (mg) | |
	Initial	Maintenance
Gabapentin	100 qhs	600-1200 tid
Amitriptyline	10 qhs	10-75 qhs
Doxepin	10 qhs	10-75 qhs
Nortriptyline	10 qhs	10-75 qhs
Hydrocodone†	5 every 4-6 h prn	5-10 every 4-6 h prn
Oxycodone SR	10 every 8-12 h	10-80 every 8-12 h prn

*prn = as needed; qhs = at bedtime; SR = sustained release; tid = 3 times daily.

†Available as hydrocodone/acetaminophen, 5 mg/500 mg and 10 mg/500 mg formulation. Total acetaminophen dose should not exceed 4 g per 24-h period.

Figure 1- **Drug Therapy for CRPS.** Some of the dosages and drugs currently utilized for treatment of CRPS. Patients are subject to a plethora of treatments, each of which varies based on individual patients (Rho et al., 2002).

TRADITIONAL TREATMENTS

Gabapentin

One of the most commonly prescribed and effective drug treatments for CRPS is the anti-epileptic drug, Gabapentin, which has traditionally been used for its role as an anti-conversant (Chadwick, 1992). Although initially only used to quell epileptic seizures, patients taking Gabapentin started noticing its potential use against neuropathic pain and hyperalgesia. Initially the mechanism of action and scope of potential uses of gabapentin remained a mystery, which fueled several studies into the drug's use in CRPS. In 1999, a study by Dr. Anton van de Vusse investigated 58 adults diagnosed with CRPS type 1 all experiencing a pain score greater than 3 out of 10 (Vusse, 2004). All of the patients had previously been unsuccessfully treated with opioids, non-steroidal anti-inflammatory drugs, or sympathetic block.

The double blind treatment consisted of a 3 phase trial in which group A received gabapentin followed by a washout period, followed by a placebo. Group B's treatment was the opposite starting with the placebo and concluding with Gabapentin. The "medication" period, which was either the placebo or Gabapentin, lasted 3 weeks followed by a 2 week washout period sufficient enough to expel any of the drug from the system. Patients were evaluated at three, five, and eight weeks after the onset of treatment for various pain criteria.

Patients were asked to present a global perceived effect, essentially recording how they felt overall, as well as a 1-10 neuropathic pain score. The affected limbs were also tested for nerve sensibility and allodynia through administration of pressure to the affected area.

The results showed a significant reduction in global perceived pain relief during the Gabapentin treatment. 47% of the patients on the gabapentin treatment reported that they experienced a reduction in pain, while only 17% of the patients taking the placebo experienced a reduction in pain (Figure 2). However the reduction in perceived pain was only seen in the group that took Gabapentin first, followed by the placebo. Group B, those that took the placebo first, did not experience as significant reduction in pain.
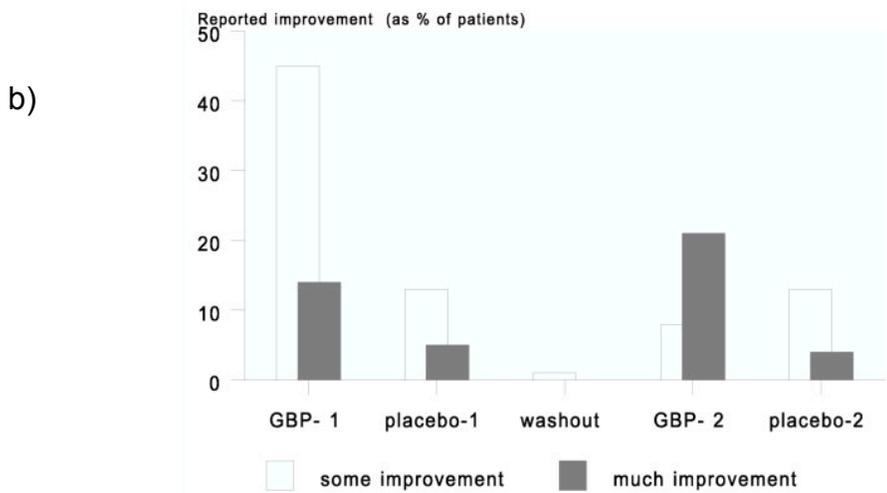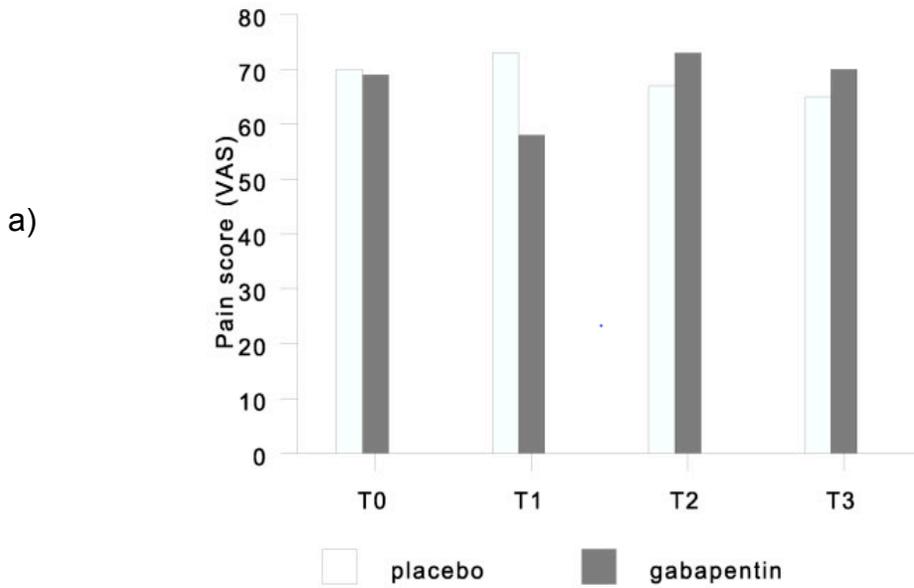
a)

b)

Figure 2-The Effect of Gabapentin on Global Perceived Pain- a) A comparison of reported pain relief between gabapentin and the placebo. B) A statistically significant percentage of patients experienced a reduction in perceived pain on Gabapentin (Vusse et al., 2004)

Additionally the results showed a significant reduction in the sensory overstimulation in the Gabapentin users. CRPS patients are often afflicted with hypersthesia, an increased sensation to the skin, which was shown to be dramatically reduced in the Gabapentin users. The results suggested that Gabapentin has a mild effect on pain but an even greater effect on the hypersthesia associated with neuropathic pain (Vusse, 2004).

The study above suggests Gabapentin as a treatment option for CRPS; however it falls short of providing a standalone effective drug therapy. In 2005, Dr. Gilron et al., investigated a joint therapy option using morphine in conjunction with gabapentin in an effort to illuminate some of gabapentin's analgesic properties (Gilron, 2005). The experiment used 4 research groups, each of which received daily doses of either placebo, morphine, gabapentin, or both gabapentin and morphine. The study looked solely at pain using the traditional 1-10 pain score as the quantifiable data and had a sample size of 41 patients, all suffering from neuropathic pain. The results showed an incremental decrease in pain from baseline to placebo, gabapentin, morphine, and finally gabapentin and morphine (Figure 3).
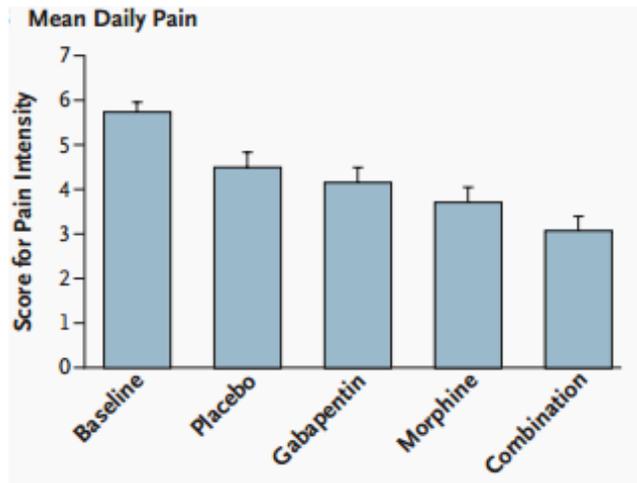
Figure 3: Gabapentin and Opioid use on Pain- A dramatic decrease in pain score from 5.72 to 3.06 when comparing baseline and a combination of gabapentin and morphine (Gilron, 2005).

Furthermore, the combination of the two drugs produced a lower pain score on Short-Form McGill Pain Questionnaire than either drug on its own. As a result of taking less of each of the two drugs on their own, when morphine and gabapentin are used in combination the side effects of each drug are dramatically reduced. This is reflected in the Short-Form McGill Pain Questionnaire, which takes into account pain felt during everyday activities and adverse side-effects (Gilron, 2005).

At this point, gabapentin has been established as a drug of choice in CRPS treatment. The side effects associated with the drug are minimal, especially when compared to those of some of the other drugs used to combat CRPS. Furthermore, the drug has been shown to alleviate pain on its own, but has also been shown to be especially effective when used in conjunction with

other interventions, most notably opioids. While not a cure, gabapentin should be one of the first tools physicians use to manage CRPS, especially if opiates are included in the treatment plan.

Antidepressants

Chronic pain conditions and the discomfort associated with them has a link to major depression. The link between depression and pain has been well established, and the use of selective serotonin reuptake inhibitors (SSRI) remains the gold standard treatment option (Blair, 2005). However, the use of tricyclic antidepressants (TCA) and serotonin and norepinephrine reuptake inhibitors (SNRI) provide other pharmacological options in the intervention of neuropathic pain.

A literature review conducted by Dr. Matthew Blair summarizes the connection between major depression and pain (Blair, 2003). The study examines a wide range of research studies from 1966 until 2002 that included both depression and pain as quantifiable data in a clinical trial. Half of the data was categorized by subjects presenting with depression and then subsequently assessed for pain, and the other half as subjects presenting with pain and then assessed for depression. The results showed that 52% of patients presenting to pain clinics, were determined to have major depression (Blair, 2003). Furthermore, 27% of patients presenting with pain were determined to also show

symptoms of depression, when treatment took place at a primary care facility. The strong difference between patients receiving a depression diagnosis after treatment at a pain clinic versus a primary care facility demonstrates the significant psychological effect of chronic pain. Typically patients who are receiving treatment in a pain clinic have dealt with their pain for some time and have exhausted traditional treatment outlets such as urgent care facilities, hospitals, and primary care. By the time treatment has been handed over to a pain specialist, the patient is familiar with their pain and its effect on their life.

Dr. Blair's review also looked at the connection between pain improvement and secondary improvement of depression, while receiving treatment for only pain (Blair, 2003). Although the data is hindered by a small sample size and uncontrolled studies, the results clearly demonstrate that improvement in depression and pain during treatment correlate with one another. What is more interesting is that all but 4 of the studies investigated by Dr. Blair used TCA as the antidepressant of choice during treatment.

TCAs are a class of compounds known as tertiary amines that function in the synaptic cleft (Sindrup, 2005). The main method of action by which these compounds treat neuropathic pain and CRPS is through their ability to inhibit the reuptake of serotonin and noradrenalin from the synapse, back into the pre and postsynaptic neuron (Sindrup, 2005). There has been some small evidence that TCA's also show some binding properties to opioid receptors, which would help to explain why pain patients experience relief under TCA treatment, however the

binding affinity is too low to be a realistic source of pain alleviation (Hall, 1981).

The leading evidence as to how TCA's function in neuropathic pain treatment is

through reuptake inhibition as mentioned, and the inhibition of voltage gated

sodium channels (Lavoie, 1990).

The efficacy of TCA treatment is a stark contrast to the results collected

from the use of SSRI's for neuropathic and chronic pain. SSRI treatment has

been shown to be unsuccessful for pain in 1992 by Dr. Max and colleagues when

they compared the results of 3 different antidepressants for the treatment of

neuropathic pain, specifically in patients suffering from diabetic neuropathy (Max,

1992). Two double blind crossover studies were conducted, one of which

compared Amitriptyline, an antidepressant of the TCA class, with a

norepinephrine reuptake inhibitor, Desipramine, which is also a TCA

antidepressant. The other group received the SSRI, Fluoxetine or a placebo.

The patients who took either of the TCA class antidepressants experienced a

pain relief at least 20% greater than the placebo group. However, only 48% of

the experimental group that received the SSRI reported mild pain relief which is

not statistically significant from the 41% of the placebo group that reported mild

pain relief. This suggests any drug in the TCA class can be utilized as an

effective treatment option for neuropathic pain; however the SSRI class of

antidepressants does not exhibit the same properties (Max, 1992). The efficacy

of both TCAs and SNRIs in treating neuropathic pain opens the door to further

investigation of norepinephrine's specific mechanism in pain alleviation.

The typical treatment course for a CRPS patient involves not only the use of antidepressants but opioids as well. The severity of pain and hyperalgesia associated with CRPS makes the use of opioids a cornerstone in treatment. Of interest is the interaction between opioids and antidepressants and how they function together when combating pain. A comparative study between opioids and antidepressants for neuropathic pain yielded supporting results for opioid, antidepressant, and joint treatment. The double blind study, conducted by Dr. Raja and associates, compared treatment between seventy-six patients affected with postherpetic neuralgia, which is a condition characterized by nerve pain following shingles, varicella zoster viral infection (Raja, 2002). Each of the seventy-six patients in the study underwent an eight week treatment period with morphine, desiparamine, and placebo. The traditional 0-10 pain scale was used as a quantitative measurement as well as a 0-100 percentile scale of overall pain relief. Both the opioids and the TCA showed an effective reduction of pain (1.9 and 1.4 respectively) over the placebo (0.2); however more interesting is that the opioids fell short of showing a statistically significant advantage in pain relief over the TCA. Furthermore, when the opioid and antidepressant were used in conjunction, 38% of patients experienced pain relief versus the 11% in the placebo group (Raja, 2002).

The significance of these results once again shows that antidepressants, in particular TCAs, are an effective treatment option for CRPS and neuropathic pain. It is interesting to note here that of the patients that completed the opioid,

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antidepressant, and placebo treatments, 54% preferred the opioid and only 30%

preferred the antidepressant treatment. The preference for the opioid treatment

could be explained by the euphoric side effects of opioids of which

antidepressants do not exhibit. The greater takeaway however is that opioids

and antidepressants appear to act independently of each other and can be

synergistic. This would indicate that an effective course of treatment for CRPS

would include both opioids and antidepressants.

Sympathetic Block

In order to understand how a sympathetic block might alleviate the pain

felt by peripheral nerve injury, it is necessary to understand how nerve injury

causes pain to begin with. Normally, pain is an evolutionary response to a

stimulus that causes damage to the body. Pain is protective in that it alerts the

body that whatever action taken is detrimental and thus should be avoided.

Additionally, pain caused by an inflamed or damaged area prevents further

manipulation before the body has had a chance to heal. Neuropathic pain

however is the result of an injury to the peripheral nerve, dorsal root, or the

central nervous system, which often times causes prolonged, chronic pain

(Woolf, 1999). Neuropathic pain offers no biological advantage and is simply a

maladaptive response by the body to lesions in the peripheral or central nervous

system (Dworkin, 2003). Sympathetic block has been investigated as a potential

treatment option for neuropathic pain since the First World War. In the simplest

form, sympathetic block is the administration of an anesthetic to block the

sympathetic nerve supply (Loh and Nathan, 1978).

One of the major limiting factors in the analysis of sympathetic block and

CRPS is the degree to which the treatment has been studied. Very few credible,

double blind studies have been conducted investigating the extent to which the

treatment actually alleviates pain in patients with CRPS. However in 1988, Dr.

Price compared the use of lidocaine versus saline when blocking sympathetic

ganglia (Price 1998). Patients provided a pain score before and after blockage

and kept a pain diary for a week after treatment. Unfortunately there was no true

control group as each patient received both the lidocaine and the saline block.

Each patient recorded massive reduction in pain 30 minutes after treatment with

both the saline (68.7% reduction) and lidocaine (74.4% reduction). The results

are not statistically significant for the lidocaine block, suggesting a strong placebo

effect. However, the study did produce some optimistic results in the duration of

pain relief. The diary data noted a significantly prolonged period of relief after the

lidocaine versus the saline injection (3 days 18 hours versus 19.9 hours) (Price

1998).

Although, the highly reported pain relief experienced by the saline placebo

group questions the results of this study, the statistically significant duration of

pain relief between the two groups is encouraging. This would suggest that

sympathetic block may not acutely alleviate pain, but may play a role in chronic

pain reduction. It is important to note the limitations of this study however. The fact that each patient received both treatments could generate a bias in the reporting of acute pain reduction. If the patients experienced pain relief after the lidocaine treatment, they may have reporting bias after a subsequent saline treatment. Furthermore, a sample size of 7 CRPS patients for the study doesn't generate enough data for confident reporting.

Extremely few studies investigating sympathetic block and neuropathic pain have been conducted, and even fewer have been done looking specifically into CRPS. This limitation, as well as the ambiguous clinical and research data, makes drawing any conclusions for sympathetic block difficult.   One of the most comprehensive studies on the efficacy of intravenous regional sympathetic block for RSD was conducted in 1995 by Dr. Alejandro Jadad. The diagnostic criteria for the study were set to include only patients suffering from severe cases of RSD and included the symptoms: persistent pain, hyperesthesia, edema, hyperhidrosis, color changes, and a history of injury that typically causes RSD (Jadad, 1995). Guanethidine, an antihypertensive drug that travels across the sympathetic nerve membrane, was used for blockage. Three different study groups were utilized: a high does guanethidine group, low dose guanethidine group, and a saline placebo group. Injections were administered once a week, unless pain relief did not occur, in which the next scheduled treatment was postponed until results were seen. Patients were asked to rate their pain severity and pain relief after each injection. Pain scores were ultimately converted into a

percentage of pain relief that was used as the primary data point for analysis.

Ideally patients would be administered an initial sympathetic block and would experience total pain relief, at which point no further injections would be necessary. Surprisingly this result did occur in one of the sixteen subjects; however that patient is an outlier. Five of the sixteen patients had to withdraw from the study due to hypotension, dizziness, and bradycardia experienced immediately after the first block, and lasting up to 24 hours. The prevalence and severity of side effects and other minor complications arrested the study early for eight of the sixteen patients, leaving only 50% of the original sample group to provide complete data. However, even of the patients that went on to finish the double blind trial, none of them reported a pain relief percentage greater than 30% of the maximum. Even worse, the severity of the side effects leads one to question the use of sympathetic block for pain relief at all (Jadad, 1995).

Although a common practice today, the experimental data behind sympathetic block as a possible treatment option for CRPS has shown confusing and conflicting results. As mentioned above, studies have not shown a statistically significant advantage of sympathetic block over the placebo and have even been shown to cause detrimental effects. Other studies have shown sympathetic block with the use of lidocaine to significantly decrease pain in CRPS patients (Wallace, 1964). Conflicting reports and the limitation caused by the lack of studies leaves sympathetic block more of a mystery than a potential treatment option, however its use continues today.

Opioids

Opioid treatment for acute pain is widespread and highly effective for both neuropathic and nociceptive pain. With the hyperalgesia associated with CRPS, the use of opioids in the form of morphine, hydrocodone and oxycodone is unavoidable; however the chronic nature of CRPS suggests other treatment options as a more permanent solution to alleviate the symptoms of CRPS. Opioid tolerance and addiction are two issues that continue to plague CRPS treatment and the healthcare field as a whole. The CDC reports that in 2012, 2 million people used prescription opioids non-medically and in 2008 there were almost 15,000 deaths as a result of prescription pain abuse (CDC, 2008) (Figure 4). Although effective, the potential abuse and damage of opioids should eliminate their chronic use from the treatment plan for most cases of CRPS. Only the most severe cases and under strict observation should opioids be administered in a long-term treatment plan.
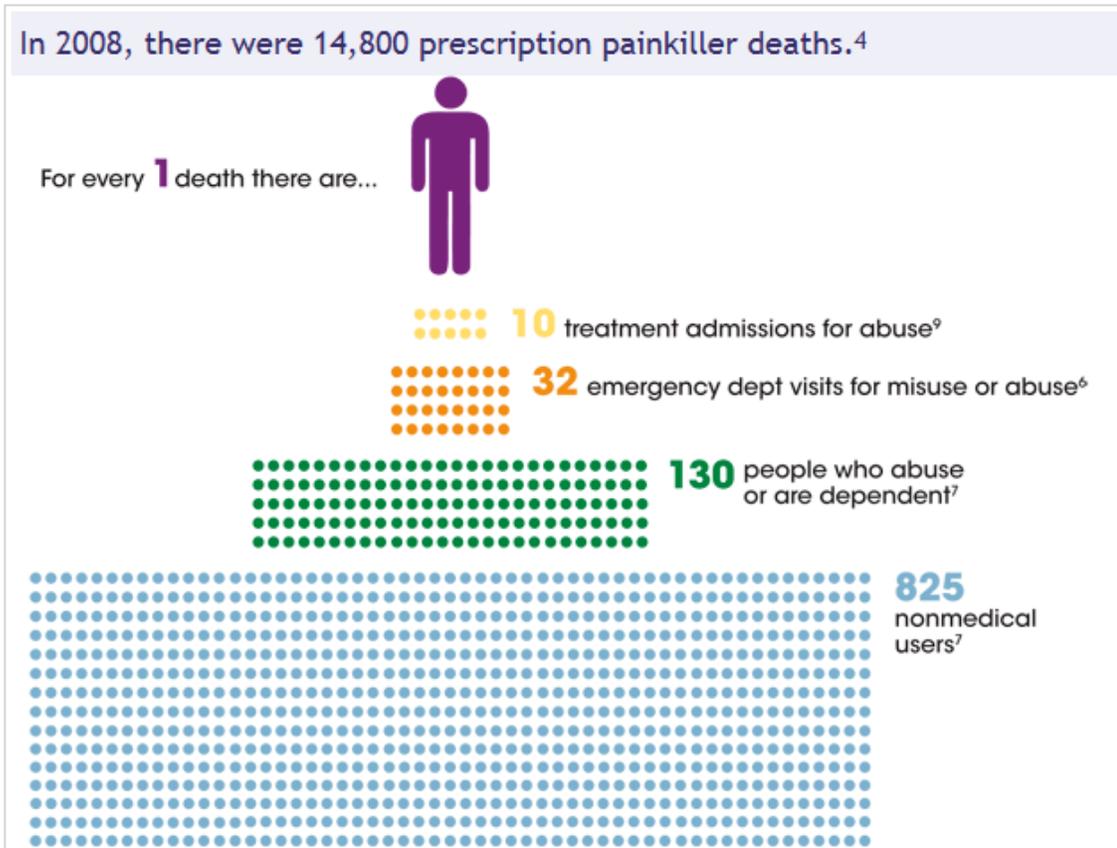
In 2008, there were 14,800 prescription painkiller deaths.[4]

For every **1** death there are...

10 treatment admissions for abuse[9]

32 emergency dept visits for misuse or abuse[6]

130 people who abuse or are dependent[7]

825 nonmedical users[7]

Figure 4: Prevalence of Opioid Abuse: The growing trend of non-prescription opioid abuse is on the rise. These numbers show the severity of the issue and the rationale as to why the chronic and even acute perscription of opioids should be heavily monitored (CDC, 2008).

Tolerance is defined as a reduced sensitivity to a drugs effect, which can occur by several different pathways (Kieffer, 2002). The leading theory as to how opioid tolerance develops hinges on the concept that opioid receptors become desensitized to the drug after prolonged exposure, thus diminishing binding of the ligand to the receptor. On a molecular basis, the classic model for opioid

tolerance involves the phosphorylation of the opioid receptor and the binding of

the compound, arrestin (Kieffer, 2002). These two actions result in the

uncoupling of the receptor to the intracellular G proteins. Additionally, tolerance

can result from a reduction in the amount of receptors present on the surface of

the cell's plasma membrane. Receptors are internalized and broken down within

the cell, resulting in fewer available surface receptors to bind opioids in the

synapse (Figure 5). The current theory is that tolerance results from a

combination of these two events. Furthermore, the initial response of the cell to

opioid binding reduces cAMP levels, however after prolonged exposure opioid

binding paradoxically results in increased cAMP within the cell (Kieffer, 2002).

Although still unclear how this reversal might affect tolerance, the increase in

cAMP has been shown to play a role in opioid withdrawal symptoms (Kieffer,
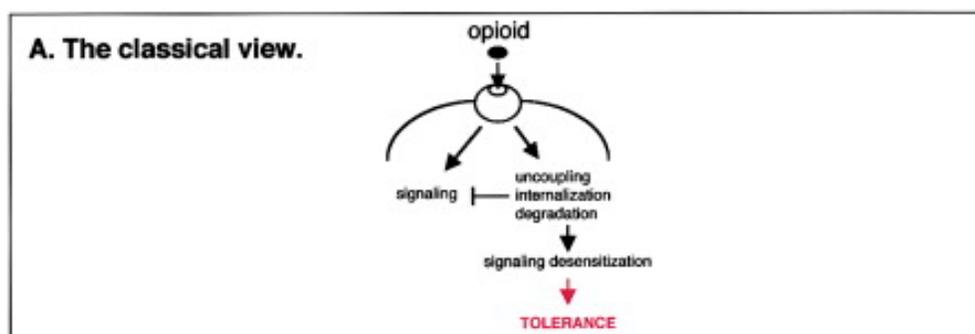
2002).

Figure 5: Opioid Binding and Internalization: As opioid ligands continually bind to
the receptor, uncoupling of the receptor to G proteins is triggered, resulting in
decreased activity and receptor internalization (Kieffer, 2002).

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The above theory provides a neat and simple conclusion to the question of how opioid tolerance arises, however recently a paradox involving morphine's binding to opioid receptors has caused some to take another look at how tolerance develops. The morphine paradox came to the forefront after prolonged morphine exposure showed that binding does not result in receptor internalization (Conner, 2004). In actuality, some opioids do not result in receptor internalization, while others, like heroin, do. Additionally, there may be several different forms of the opioid receptor in the brain, thus making specific interaction across all opioids more complex than originally suspected.

The question of how opioid tolerance arises is extremely complex and for now remains controversial. The specific interactions of different opioids to different receptors in the brain still eludes our understanding today, and thus their use should be closely monitored when administering over a long period of time. There is no question that opiates are effective and should be used as an acute treatment option for CRPS; however tolerance and our ignorance to its manifestation argue against chronic opioid treatment.

One of the most troubling side effects of prolonged opioid exposure is the possible development of the exact symptom opioids are trying to combat: hyperalgesia. Traditionally, the relationship between pain and opioid treatment has followed a linear trend: the more pain experienced, the more drug administered. Patients suffering from chronic ailments such as cancer and CRPS may require large doses of opioids over a prolonged period of time, which

after an initially favorable response, may develop a paradoxical response such as hyperalgesia or allodynia (Mercadante, 2006). The metabolic theory behind this phenomenon involves the activation of N-methyl-D-Aspartate (NMDA) receptors in the CNS. NMDA activation leads to an increase in intracellular calcium, which then activates protein kinase C and increases the intracellular level of nitric oxide. It has been shown that activation of protein kinase C and increased levels of nitric oxide can lead to hyperalgesia and pain states (Mercadante, 2006). However, very little experimental data has been conclusive on what is occurring with opioid-induced hyperalgesia. This shortcoming again limits our understanding of prolonged opioid use.

Ketamine

Ketamine infusion treatment targets the NMDA receptor. NMDA receptor antagonists have been shown to inhibit the hyper excitability of nociceptive neurons in the spine, thus making NMDA receptors a primary target for pain suppression (Petrenko, 2003). The investigation of NMDA receptors for pain has been relatively scarce until recently because of the complexity of pain in the human body versus animal models. Historically, the application of successful pain treatments, such as NMDA blocks like dextromethorphan, has shown promise in animal studies, but has been complicated in human trials by the

complexity of pain and the more noticeable CNS effect that NMDA antagonists create.
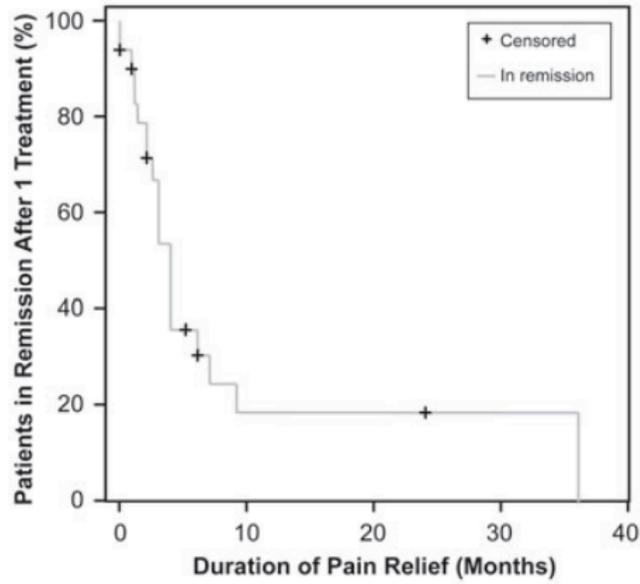
Ketamine's use in modern medicine is limited to anesthesia, where a high bolus dose produces a strong anesthetic effect. However there is significant street value for the use of ketamine in smaller doses. When snorted in small amounts, ketamine produces an effect similar to that of cocaine. Users experience brief euphoria followed by a rush of energy. However, when converted into a liquid form and injected directly into the blood stream, ketamine at higher doses produces powerful hallucination and psychotropic effects (Dotson, 1995). Users experience what is known as a "K-hole" described as falling into a median between consciousness and the subconscious state which is typically produced by the higher anesthetic doses of ketamine (Dotson, 1995). The use of ketamine as a treatment for pain thus makes it dangerous at any dose, and especially dangerous for patients with bradycardia or hypotension as the drop in blood pressure and heart rate that results from ketamine's anesthetic properties leaves patients vulnerable to fatal complications. Additionally, ketamine has been shown to be highly addictive and is currently scheduled as a class 2 narcotic with the likes of marijuana and cocaine (Dotson, 1995). The chronic abuse of ketamine has led to lower urinary tract complications, which are important to note before using the drug as a treatment option. A review of 59 ketamine abusers showed wide spread cystitis, hydronephrosis, and potentially irreversible renal damage (Chu et all, 2008).

In spite of its potent neurotoxic side effects, ketamine has been shown to display promising pain alleviating properties, specifically in patients affected with CRPS. In 2005, Dr. Correll conducted a retrospective study examining CRPS I and CRPS II patients receiving outpatient ketamine infusion treatments over a 7 year period (Correll, 2005). Ketamine infusions administered at a starting dose of 10mg/hr and were increased until the patients noted a feeling of inebriation. A slow, incremental increase in ketamine is paramount in treatment as to avoid the side effects mentioned previously. Additionally, each patient has a different optimal dosage before the onset of side effects, thus making ketamine treatment more of a continuum than a standard dose. Patients provided a pain score and duration of pain relief, which was noted after each treatment for a maximum of 48 hours. Of the 33 patients included in the study, all of them experienced pain relief immediately after both the first and second treatment. Additionally, 54% of patients experienced 3 months of pain relief after the first infusion, and 31% experienced pain relief after 6 months (Figure 6).

These results illuminate how powerful ketamine treatment can be for the relief of CRPS pain, however it is important to note the unintended effects each treatment had on the patients. Side effects were experienced in all 33 patients. The most commonly experienced effects were inebriation, nausea, dizziness, and blurred vision. As noted before, ketamine has extremely powerful CNS effects and although effective, treatment can be taxing on the patient. Furthermore 6 of the 33 patients experienced hallucinations and although none

of the patients in this study developed addictive behavior, widespread application of the treatment leaves room for addiction as an unwanted secondary development. One troubling observation noted by researchers in the study shows that the onset of inebriation is essential in determining the optimal therapeutic dosage, which again leads back to the issue of exposing patients to a potentially addictive, powerful narcotic.   It should also be noted that four patients developed elevated liver enzymes after the first ketamine infusion, making careful monitoring of hepatic function essential for ketamine treatment. The success of ketamine in alleviating pain in this study cannot be ignored, however the wide range of severe side effects hinder ketamine's use to a tightly monitored in-patient treatment option.
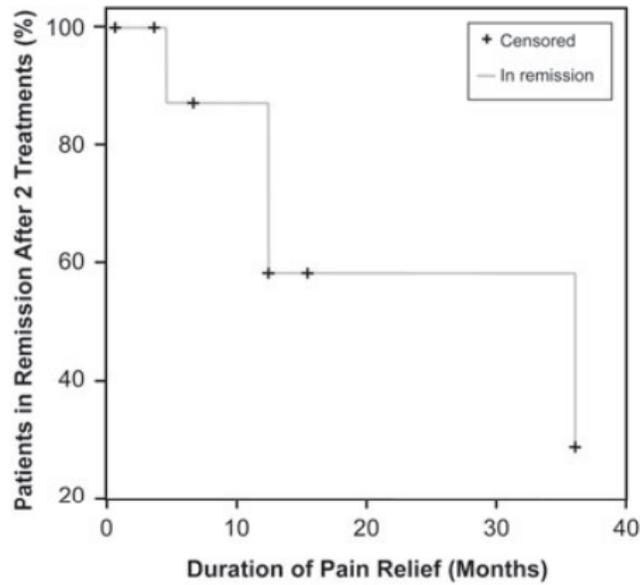
a)

b)

Figure 6: Ketamine Infusion Pain Relief: a) patients experiencing pain relief after the first infusion started at 100% and maintained some pain relief for almost 40 months. b) Duration of pain relief after a second ketamine infusion (Correll, 2004)

Another study, conducted by Dr. Robert Schwartzman in 2009, achieved a more robust experimental set of criteria when examining ketamine's use for CRPS (Schwartzman, 2009). The study was engineered to only include severe cases of CRPS. Patients had to have exhibited symptoms for a minimum of six months and had failed to respond to previous pharmacological interventions (opioids, NSAIDS, antidepressants, and muscle relaxants). Before any treatment had started, every patient registered a baseline pain score through an extensive pain questionnaire including severity of pain, duration, location, degree, and effect on daily activity. Dr. Schwartzman noted responses to different pain stimulants including: thermal, deep pressure and finger tap. Both the ketamine and placebo group were administered treatment for a duration of 10 days, with data being collected after 5 initial days, 2 days off treatment, and then again after the final 5 days of treatment.

The overall scope of this experiment is extensive and provides the best data to available to date of ketamine's treatment potential. Data from the 26 patients included in the study demonstrate a statistically significant reduction in pain across every variable investigated (Figure 7). More interesting, is the lack of pain relief experienced by the placebo group. Unlike sympathetic block with lidocaine, the control group here reported no change in pain score throughout the treatment, thus eliminating any potential bias (Schwartzman, 2009).

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Figure 7: Pain Reduction in Ketamine over Placebo: A graphical representation of the statistically strong advantage ketamine has over the placebo in reducing pain experienced from CRPS (Schwartzman, 2009)

Clearly from the data complied to date, the use of ketamine as a treatment option for CRPS is extremely promising. Widespread application of ketamine is hindered by the strong side effects associated with the drug and by the lack of credible, double-blind studies conducted. As of 2009 Dr. Schwartzman's study of 26 patients was the only study into ketamine's use in CRPS that utilized a control group. It is possible that physicians are hesitant to turn to ketamine because of

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its dangerous side effects; however the nature of severe CRPS cases demands radical and progressive treatments.

EXPERIMENTAL TREATMENTS

Naltrexone

While only just recently investigated, low dose naltrexone has quickly emerged as a potential treatment option for CRPS (Chopra, 2013). The theory behind the use of naltrexone centers on the neuroinflammatory characteristics of CRPS. Once CRPS has progressed pass the use of traditional treatment options, suppression of the neuroinflammation causing hyperalgesia and CRPS symptoms becomes paramount. The activation of inflammation is brought on by the upregulation of TLR4 (Toll-Like Receptor 4) in microglia (Chopra, 2013). It has been shown that upregulation of TRL4 has directly resulted in neuropathic pain, thus making the downregulation of TRL4 a prime candidate for the relief of neuropathic pain and subsequently CRPS. The upregulation of TRL4, through several molecular pathways, results in the release of cytokines, which cause pain. Naltrexone is a TRL4 antagonist and serves as an option for the downregulation of TRL4.

Traditionally, naltrexone has been used as an opiate antagonist. Heroin

abusers on the verge of overdose are administered naltrexone as a way to

reverse the severe bradycardia and lethargy experienced. Recently Dr. Chopara

noted the current cases in which naltrexone were used for CRPS (Chopra, 2013).

It is important to note that the treatment dosage of naltrexone used for CRPS is

of an order of magnitude 50 times less than that used to combat opiate overdoes.

A 46-year-old male suffering from severe CRPS for 4.5 years (Figure 8) was

administered low doses of naltrexone after he had reported a pain scaling 10/10.

After 2 months of treatment the pain fell to an average of a 5 or 6 out of 10 and

the use of his cane (which he had used for 6 years) was no longer necessary.

The patient experienced resolution of the ulceration on his leg as well as a

marked increase in quality of life (Chopra, 2013).

Figure 8: **Physical Presentation of CRPS in Lower Limb**: (a) Severe CRPS and ulceration (b) in a patient prior to low dose naltrexone treatment (Chopra, 2013)

Another case of low dose naltrexone use involves a 12-year-old female suffering from color change, allodynia, and increased temperature of the affected limb. Pain in the patient was reported at a minimum of 8/10 and a maximum of 10/10. After starting a treatment of 3mg naltrexone three times a day the dosage was increased to 4.5mg after 4 weeks. Incredibly, the patient's reported pain dropped to between 3 and 5 out of ten, complaints of alldynia diminished, and

temperature stabilized. Additionally, the patient underwent surgery to correct destabilization in her ankle as a result of a pervious condition. Following surgery, the use of low dose naltrexone was shown to have a greater effect on alleviating pain over oral opioids. Astonishingly, after 18 months of naltrexone treatment, all symptoms of CRPS in the patient resolved with zero side effects reported.

It is still unclear what the direct cause of the hyperalgesia and allodynia experienced by CRPS patients, however the success of low dose naltrexone supports the growing belief that neuroinflammation is the culprit. The suppression of overly active glia cells through naltrexone's antagonistic properties and the subsequent decrease in the spread of neuroinflammation is promising for the treatment of CRPS.

Thalidomide

Thalidomide was made popular in the 1950's as an anti-anxiety and anti-nausea medication prescribed mostly to pregnant women. The use of thalidomide became widespread in Germany when the drug became available without the need for a prescription. However, proper testing had not been conducted on the effect the drug has on a developing fetus, a misstep that resulted in thousands of children being born with birth defect after being exposed to thalidomide in the womb. This shelved the use of thalidomide for a long time,

until its application in the treatment of multiple myeloma was discovered.

Thalidomide, in conjunction with chemotherapy, has been shown to be effective

in containing the proliferation of B-cells through direct apoptosis and G1 growth

arrest (Frederica, 2008). During clinical trials for the application of thalidomide to

multiple myeloma, the resolution of RSD had unexpectedly been observed,

prompting some to further investigate how thalidomide might be used as a

treatment option for CRPS.

In 2003, Dr. Robert Schwartzman, while investigating ketamine's use in

CRPS, conducted a study investigating thalidomide's treatment capability in 42

CRPS patients (Schwartzman, 2003). All 42 patients met the International

Association for the Study of Pain diagnostic criteria mentioned earlier and had all

failed pervious intervention. The treatment dose of thalidomide was kept

extremely low to start and none of the patients were pregnant, thus ensuring

none of the negative properties of thalidomide's use could be seen here. Dr.

Schwartzman used pain relief, healing of lesions, and increased function as the

data points for the study. 17% of the 42 patients experienced a dramatic

response in pain relief and an additional 14% reported some relief. Side effects

included rash, pain, edema, and solmnolence, all of which could be treated and

prevented by using a lower dose of thalidomide (Schwartzman, 2003).

The results of Dr. Schwartzman's study show that thalidomide has the

potential to be a treatment option for CRPS. The highly advanced CRPS

patients used in this study had received all conventional treatments, thus making

the 17% that did experience drastic pain relief extremely promising. The limitation with thalidomide, as we have seen with the majority of non-conventional CRPS treatments, is the severe lack of experimental evidence. More controlled, double-blind studies need to be done as well as more observational clinical data into the use of these experimental treatments. Thalidomide's role in causing birth defects makes its use extremely dangerous and thus should only be administered in a tightly controlled setting. Additionally, the negative side effects experienced by patients as a result of an elevated dosage should again render thalidomide's use to a clinical setting.

Vitamin C

Vitamin C may not instinctually seem to play a role in CRPS; however recent studies appear to indicate that ascorbic acid (vitamin C) can act as a preventative measure against CRPS. Dr. Paul Zollinger and his team have been investigating ascorbic acid's preventative properties in CRPS for almost 15 years and have reported promising results based on several clinical trials (Zollinger, 1999). Vitamin C's potential role in CRPS treatment is fueled by the role oxygen radicals play in the pathogenesis of CRPS. The belief that oxygen radicals are responsible for the sympathetic microcirculatory disturbances experienced in the initial development of CRPS, served as the inspiration for Dr. Zollinger's use of

vitamin C. Furthermore, it has been shown that vitamin C acts on the epithelial cells of the microvasculature to prevent capillary permeability and edema (Tanaka, 2000). The methodology of vitamin C's actions on the microvasculature of epithelial cells comes from the reduction of lipid peroxidase, which has been shown to increase vascular permeability following burns. Furthermore, vitamin C is an anti-oxidant that breaks down lipid peroxide, through the activation of vitamin E.

Microvascular permeability and leakage following a trauma does not directly result in CRPS, however the secondary inflammation that follows can. This is where vitamin C's ability to prevent leakage and edema connects to CRPS. Edema is followed by inflammation, and as noted previously, inflammation of peripheral nerves can lead to CRPS. If vitamin C is able to reduce the microvascular damage associated with the limb traumas that typically give rise to CRPS, theoretically its use as could greatly reduce the instance of CRPS.

The first clinical trial investigating ascorbic acid's preventative properties was a simple comparison measuring the rates of post-traumatic RSD in patients with wrist fractures. The experimental group was treated with 500mg ascorbic acid from the time of the injury until a period of 50 days. The other group received a placebo in parallel with the experimental group. Patients in both groups were treated for a period of 50 days, and evaluated for one year, during which RSD was diagnosed upon the presence of four of the following six

symptoms: unexplained diffuse pain, redness of the skin, increased temperature of the skin, diffuse edema, limited motion, and the onset of any of these symptoms upon physical activity.

In total 146 patients were participated of which 57 received vitamin C treatments. It can be seen from Figure 9 that wrist dominance, fracture type, and side of the fracture do not play a role in RSD development. However, sex appears to be a significant variable in the patients that did develop RSD. Furthermore, it was noted that all of the female patients were postmenopausal; suggesting that estrogen level or even osteoporosis could be areas of future research. It is not surprising though that more women developed RSD, as this is typical of the CRPS demographic. Of the patients taking the vitamin C treatment, only 4 developed RSD, while 14 of the 51 patients taking the placebo developed RSD. The most striking, and promising, statistic comes from the comparison of the patients who did develop RSD. 22% of the patients who developed RSD were on the vitamin C treatment, while a striking 78% were in the placebo group (Zollinger, 1999).

Characteristic	RSD (n=18)	No RSD (n=101)	Relative risk (95% CI)
Sex			0.22 (0.03-1.58)
Male	1 (6%)	24 (24%)	
Female	17 (94%)	77 (76%)	
Side of the fracture			0.74 (0.31-1.78)
Right	7 (39%)	48 (47.5%)	
Left	11 (61%)	53 (52.5%)	
Dominance			1.31 (0.56-3.10)
Yes	10 (56%)	48 (47.5%)	
No	8 (44%)	53 (52.5%)	
Fracture type			0.37 (0.16-0.89)
23-A	7 (39%)	68 (67%)	
23-B+C	11(61%)	33 (33%)	
Reduction	11 (61%)	59 (58%)	1.10 (0.46-2.64)
Complaints in plaster	12 (67%)	18 (18%)	0.17 (0.07-0.41)
Therapy			2.91 (1.02-8.32)
Vitamin C	4 (22%)	50 (50%)	
Placebo	14 (78%)	51 (50%)	

Figure 9: A Controlled Study of Vitamin C's Preventative Potential in RSD:
The results of Dr. Zollinger's double-blind study show relatively standard outcomes with the exception of the remarkable difference between RSD patients receiving vitamin C treatment (Zollinger, 1999).

Dr. Zollinger followed up his 1999 study by conducting an additional experiment, again using wrist injury as a precursory trauma in CRPS development (Zollinger, 2007). The results mirrored those of the previous study,

again showing a strong statistical advantage in the prevention of CRPS from the use of high dose vitamin C. Dr. Zollinger's data suggests that vitamin C can be used as a low-risk, preventative treatment for the development of CRPS, following minor trauma to the limbs. Based on vitamin C's known ability to prevent edema and microvascular capillary leakage, the reduction in inflammation and subsequent neuroinflammation following trauma holds strong potential to the prevention of CRPS. Additionally, the use of high dose vitamin C doesn't propose any adverse effects to patients following trauma to the limbs. It is already recommended by the FDA that persons greater than age 19 consume at least 90mg of vitamin C a day, and the risk of overdose is extremely low. A standard treatment plan for CRPS is still yet to be established, making disease resolution difficult. If prevention is at all possible, a 50 day vitamin C course would seem prudent following limb trauma.

High Dose Capsaicin

Capsaicin is the active ingredient found in chili peppers, which is responsible for their notorious burning sensation. When put in contact with the skin, even very low doses of capsaicin are known to cause an intense and unpleasant burning (Robbins, 1998). The burning sensation experienced by the initial application of capsaicin to the skin is the result of the excitation of neurons

which is then followed by a period of enhanced sensitivity (Mason, 2004). Following a period of hypersensitivity and neuron excitability is a refractory period marked by desensitization. In patients with neuropathic pain, especially those experiencing hyperalgesia, a period of desensitization could result in the alleviation of pain.

Although capsaicin has been studied for the alleviation of pain before, only one study has investigated its specific use in CRPS. Capsaicin creams were concentrated to one of four experimental doses: 0.05, 0.075, and 0.10 percent. Ten patients were selected for the study in which one of the three doses of capsaicin was applied to the area of the body experiencing hyperalgesia. Remarkably the pain associated with the capsaicin treatment lasted up to 7 days for some patients in the trial, although on a diminishing basis. Over the course of a week following the initial capsaicin treatment, 9 of the 10 patients reported alleviation in pain and increased utilization of the affected area (Figure 10). Some patients reported an increased ability to bear weight on affected limbs, while another patient reported a drop in hyperalgesia great enough to permit wearing a shoe a foot severely affected with CRPS (Robbins, 1998).
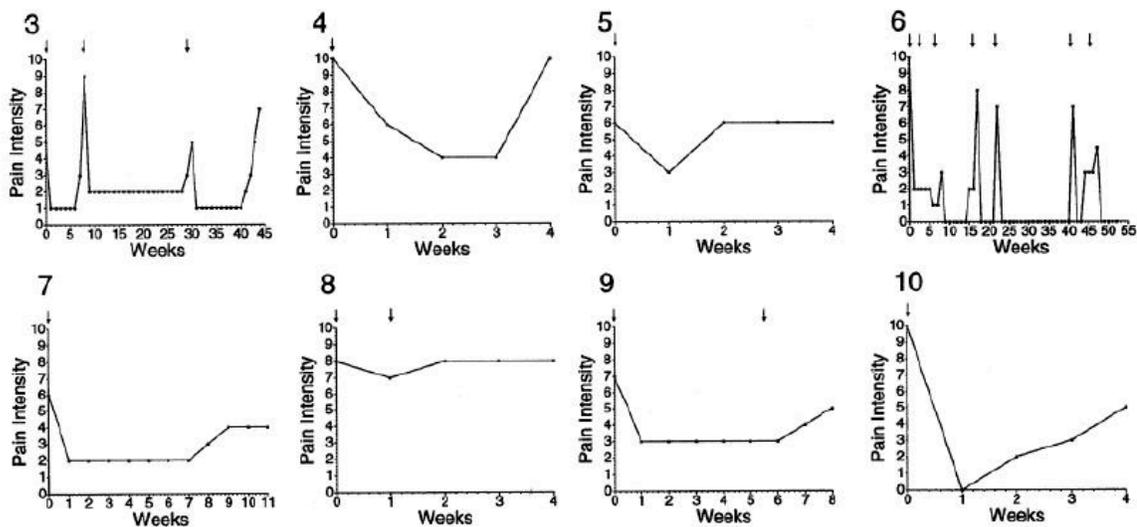
Figure 10: Alleviation of Pain Upon Capsaicin Treatment: Each graph represents one of the patients in the clinical trial for capsaicin treatment. The arrows above each of the graphs indicates the time at which capsaicin was administered. The decline in pain experienced by each patient is evident (Robbins, 1998).

The limitations of capsaicin treatments are obvious. Application of capsaicin at doses even 2 orders of magnitude higher than commercially available results in dramatic pain, which in the case of Dr. Mason's study mentioned above, treatment with opioids, became necessary for all participating patients. However in neuropathic pain as severe as CRPS, radical treatments like this have a role. Patients who have exhausted all other treatment options would be willing to undergo unconventional treatments such as topical capsaicin. As mentioned previously, CRPS manifests differently in every patient and treatment options today have varied in efficacy. Some treatments work

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especially well for some patients, while others have no effect. When trying to combat a disease as frustrating and elusive as CRPS, all treatments options should be considered on an ongoing basis. Physicians are charged with monitoring each individual treatment option and must not be afraid to change course if necessary. Until we have a firmer grasp on CRPS, a wide array of treatment options is available and must be considered.

DISCUSSION

This review has examined multiple treatment options, some that have been traditionally used for the treatment of CRPS and others that are experimental. What has been made clear is that CRPS is a dynamic disease that still escapes our full understanding. Although not a singular curable treatment exists, there is a wide range of treatment options that can be used to manage the symptoms of CRPS.

A disturbing reality of CRPS treatment is the number and severity of side effects that accompany many of the treatment options. The use of opioids is often unavoidable when treating pain of the magnitude experienced by CRPS patients. However, the ever expanding issue of opioid dependence, tolerance, and abuse cannot be ignored. Thus the niche for opioids in the treatment of

CRPS falls in the acute phase and only for short duration of utilization. The efficacy of opioids cannot be denied, however over time as tolerance builds, they lose potency and leave patients at risk for dependence and overdose. It is paramount that physicians are aware of the pitfalls associated with their use and administer them in a tightly controlled manner.

Most of the treatment options available for CRPS are hindered by negative side effects. Gabapentin eludes these limitations and has been established as one of the fundamental treatment options for CRPS. Experimental and observational data have shown that gabapentin possess pain alleviating properties, but it's the drugs complimentary relationship with other treatments that makes it such an asset for treatment. Gabapentin should be utilized at the forefront of CRPS treatment, and should absolutely be prescribed in any instance where opioids are administered. The additive effect gabapentin has on opiates diminishes the need for incremental doses and mitigates some of the dangerous side effects of opiates.

Antidepressants role in treating neuropathic pain is another highlight found from this review. Antidepressants have a strong role in combating the depression experienced by CRPS compliments their ability to also alleviate neuropathic pain. Antidepressants, TCAs in particular, exhibit minimal side effects and have been shown to intensify the analgesic effects of opioids. This makes their use both low risk and highly effective and should be a first choice when treating CRPS.

The evidence supporting sympathetic blocks for CRPS treatment is fair to poor. Promising data was invalidated by conflicting reports of lidocaine's efficacy in relieving pain symptoms. Furthermore, some of the more general overview studies of CRPS suggested the discontinued use of sympathetic block all together (Forouzanfar, 2002). From the data observed in this study, the efficacy of sympathetic block remains a bit of a mystery and requires further experimental data. Clearly some benefit has been observed in the past, as sympathetic block has been used in the treatment of CRPS for some time; however the extent of its use and optimal method of implementation requires further study.

The results of some of the new experimental treatments for CRPS are encouraging, especially the use of low dose naltrexone. Thalidomide, naltrexone, and Ketamine have all been shown to be extremely effective in alleviating pain in CRPS patients, however remain underutilized in current treatment. Ketamine has proven effective but requires close monitoring during administration. Future studies are needed on the optimal Ketamine dosage and methodology of the drug. Thalidomide and naltrexone have only just recently entered the conversation, however initial clinical trials show good results. Additional studies and observational data on these treatments have the potential to unlock a more effective treatment plan than currently available.

Finally, some of the more fringe treatments include vitamin C and high dose capsaicin. Vitamin C may be the most innocuous treatment for CRPS, even though its use is limited to a preventative role. However, with rates of

CRPS developing following fracture reaching as high as 37%, the preventative use of vitamin C is reward with little risk (Atkins, 1990). High dose capsaicin is a different story all together. This treatment is extremely painful in itself and should really only be considered for the most severe and desperate cases. Although very limited in the literature, the results reported for capsaicin's use are encouraging.

Through an evaluation of various treatment options for CRPS, it is clear that one singular treatment isn't sufficient. Each patient falls in a unique position on the spectrum of CRPS, and a specific treatment course is necessary for each individual patient. Physicians and patients are charged with the responsibility of constantly challenging and changing treatment options as they prove ineffective. It is important to note that other non-pharmacological interventions exist for CRPS. As mentioned earlier, physical therapy early in CRPS development has proven to be effective and is a staple of treatment today. Additionally, spinal cord stimulation in the latter stages of CRPS is widely used as an effective treatment. Furthermore, the volume of treatment options is enormous, which is a strong indicator of just how lost we are when it comes to CRPS (Birklein, 2005). The ambiguity surrounding the disorder has created more of a shotgun approach to treatment instead of an efficient and targeted method. Until we are able to lift the veil on CRPS, treatment has to be ever changing and evolving with each individual patient.

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