Conotoxins Reveal Significant Psychopharmacological Effectiveness: The Future of Pain Management

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Various treatment modalities of acute and chronic pain have been an area of demand and interest for centuries. This article discusses the positive and negative consequences of pharmacological treatment of pain. The literature is based on extensive review of the data gathered among the experts in the field. This study focuses on the 2 major classes of drugs that are used to control pain: opioid and nonopioid analgesics. While opioids have revealed a vast range in purpose, research has indicated the many side effects as well as tolerance that can result. Current findings suggest nonopioid treatments derived from venoms are a more effective approach for pain management. Clinical trials have yielded conotoxins a positively explosive pharmacological approach for pain management.

Many of us suffer chronic pain but what is an effective treatment? Research indicates that 80 percent of the United States adult population takes at least one drug a week to arrest pain (Mercola, 2002). Chronic pain is a long-term persistent pain often lasting months to years, and many even suffer for life despite treatment. The most frequently reported complaint by patients is chronic and persistent pain however, it is the most difficult to treat because individuals response to pain varies as well as their response to pain management.

Pain is affected by multiple subjective and often immeasurable factors. Pain encompasses the emotional state, the level of attention, personality characteristics, and past experiences of pain incidents that reflects how an individual will cope and tolerate pain. Moreover, it is important when understanding the concept of pain that the sensation of pain may be serving as a simultaneous symptom of psychological stress or even as a defense against it (Kaplan & Sadock, 1998). As a result of the number of people who report pain, take pain medications, and seek the treatment for pain, the area of pain management has increasingly become a well-researched area of medicine and related health fields.

Although there has been a tremendous growth in the field of pain management the therapeutic and treatment modalities from a pharmacological perspective, specific targeting and effective dissipation of pain still lag behind. Despite the fact that there are many pharmacological drugs that have been discovered and made available for people to take, the root or source of these drugs are very often from what we have been using for years. There are studies that yield pharmacological advances that deviate from the traditional drug therapies are near however, they are limited, many are still in clinical trials, and unavailable for the general population.

Part of what the research has indicated is that in our
attempts to treat pain we are potentially putting pain sufferers at greater risk for other problems such as addiction, tolerance, bleeding problems and even death.

Pharmacologically there are two major classes of drugs that are used for pain control: opioids and nonopioid analgesics. There is a plethora of data on the use of opioids and nonopioids and the wide range of which they serve as a treatment. There was not a drug available for pain management that is as broad in scope as opioids, until now. The focus of this study is to discuss opioids as a pain therapy, and to explore the many other nonopioids that can be utilized as a treatment for pain. In addition to the benefits of combining opioid treatment by adding an adjuvant therapy which is suggested to offer more accurate selectivity with less side effects and tolerance. Furthermore, this article is going to examine and compare the pharmacological offerings that are considered to be traditional forms of pain management specifically to venoms which are being explored, tested, and in some cases even clinically sampled as a new approach to pain management.

Venoms from venomous animals are being researched and biochemically manipulated to offer the medical field another form of pain management treatment. The venom of many animals is being tested for the potential medical benefits for humans. These advancements in medical treatment are on many levels highly significant for the overall functioning of humans. The Gila monster, a venomous creature excretes a substance in its venom that is similar to a human protein that stimulates the secretion of insulin. This venom is suggested to possibly replace insulin injections in people with elderly-onset diabetes in addition; it proclaims the prevention of the progression of the disease. Researchers have used the Eastern and Western diamondback rattlesnakes venoms as a molecular model to provide them with venom peptides to produce a synthetic material, which is used to treat high blood pressure as well as congestive heart failure. Another venom that has been reported to be medically used is the Malayan pit viper. The viper’s venom consists of components that have an anti-clotting effect. The function of this compound is to allow the blood to flow better, and help prevent blood clots in treating victims of stroke. The Thailand cobra on the other hand is being explored for several uses. This venom has indicated treatment for neurological diseases such as Alzheimer’s and Parkinson’s in addition to therapeutic drug for various kinds of cancer as well as a treatment for herpes and Cytomegalo viruses. Another snake is also found to have medicinal venom; the Russell’s pit viper, this viper has an enzyme in it that is used in the diagnostic test for Lupus. This test is known as the DVV test from American Diagnostics, Inc. Although many people are aware that snakes produce venoms there are other species that produce this toxin as well.

The Cameroon red tarantula produces venom, which immobilizes and captures small rodents and birds. This venom has revealed to have possible treatment implications for some brain cancers and neurological disorders. Yet found in another spider like creature the scorpion, the Giant yellow Israelean scorpion specifically, has had a drug derived from a substance in its venom that could keep cancerous cells in a specific type of brain tumor from migrating to other parts of the
brain. Finally, the last venoms reported to have medicinal properties is the Cone Snail. The cone snail has been reported to be a synthetic painkiller that is derived from a peptide in the animal’s venom. More specifically, conotoxins which is a venom that is derived from the magician cone snail, Conus magus, shows promise as a non-addictive pain control substance that is suggested to be 1000 times more potent than morphine in relieving pain in humans. These significant results have lead researchers to continue to explore the numerous possibilities that cone snails may offer.

As the article has indicated that there are a number of reported venoms that have properties that offer both potential medical and pain management treatments for humans. Although the scope of this study is pharmacological treatment for pain management; it will specifically explore the effectiveness of venoms as a pain manager as opposed to other pharmacological therapies that have been utilized as well as suggested to be effective to eliminate or manage pain. Previously mentioned there are numerous animal species that have been found to produce venoms that can be and some are being utilized for disease diagnosis, control, and treatment. As a result of the overabundance of material on venoms, this article will focus specifically on the cone snail venom, conotoxins and discuss the findings at greater length in addition to why this pharmacological advance might serve as a replacement of opioid treatment for pain management.

Cone snails have cone shaped shells, a fleshy foot, a head and tentacles. The have been reported to live in the Indian and Pacific oceans, the Red Sea, in the Caribbean, and along the coast of Florida. It has been reported that there are about 500 different kinds of cone snails around the world. The cone snail is reported to be a non-aggressive towards humans, that is they are not known to attack and or sting humans at random, it is unlikely that they will be seen or found by swimmers and snorkelers but they do attack sea creatures. The sting usually occurs when divers in deeper reef waters handle them. The various Conus species are known to paralyze and eat a wide variety of marine creatures including fish, worms, and other molluscs. Their way of attack is to extend a proboscis like organ with a harpoon like tip, firing venom into their prey. This action induces paralysis and death in seconds. There have been reports of cone snails killing humans who have innocently picked them up however, the number of reported fatalities is small and there is little indication of additional fatalities since the advancement of this data (O’Neil, 1996).

However, if a human is envenomed several different symptoms may occur depending on the conus species involved. Upon being envenomed pain, which may be severe, has been reported to take place as well as a spreading numbness beginning from the point of entry, and radiating numbness continues to envelop the body. In cases where there is severe envenomation, muscular paralysis ensues. Victims have a difficult time breathing and swallowing. Gag and other reflexes are absent. Blurred and double vision is reported. Recovery, if any may vary from a few hours to several weeks. There is no antivenom currently. Respiratory and cardiovascular supports are the key components to emergency care (McIntosh & Jones, 2001).

Envenomation by specific venomous species have been found to be more lethal than other venomous species. Researchers have
categorized members of the cone snail family into superfamilies helping to further identify the lethality.

The family Conidae, Turridae and Terebridae constitute the superfamily Conoidea, members of which are characterized by the possession of the venom apparatus. The most deadly are the Conidae that include approximately 500 species of the genus Conus.

The venom of some of the Pacific Ocean’s cone shells has shown extraordinary promise in controlling acute pain. A recent experiment in the United States has shown that a synthetic molecule based on one of the paralyzing neurotoxins in the venom of the magician’s cone snail, magically blocks acute pain in patients who no longer obtain relief from opiate drugs. Some of the types of patients that have been explored include terminally ill cancer and AIDS patients with chronic pain in addition to long-term amputees with “phantom limbs” (O’Neil, 1996).

O’Neil’s (1996) findings from the pain clinic at Stanford University School of Medicine in San Francisco, suggesting that the compound call SNX-111 (a conotoxin derived from the cone snail, and developed by the biopharmaceutical company Neurex) is 100 to 1000 times more potent than morphine.

Additionally, other cone snail experts report that there are now more than 70 different species on the Great Barrier Reef and many others around the Australian coast. Australian researchers who have been studying cone snail venom for more than five years have been recognized as a result of their developed of a rich cocktail of neurotoxins in the native cone snail venoms and their effect on nerves and muscles.

The cone snail venoms are enormous in their composition. Components present in the cone venoms consist primarily of proteins and peptides. The most intensely studied group, the small peptides, can be divided into two major groups. One group is the multiple disulfide bonds, referred to as conotoxins and the second group is the single disulfide linkage or none at all. Although there may be over 50,000 unique peptide sequences present in the approximately 500 cone species, the species may be generally grouped into superfamilies. Members of each superfamily have in common a highly conserved signal sequence in their sequence in the precursors. Family members within a superfamily have a characteristic arrangement of cysteine residues in their mature peptides (McIntosh, et.al, 2001).

The most extensively studied superfamilies are the A-, M-, and O- superfamilies. Peptide families found within the A-superfamily include the •-conotoxins and the •A-conotoxins, both of which are competitive nicotinic acetylcholine receptor antagonists. In addition, there are kA-conotoxins, which may act by blocking voltage-gated potassium channels. In the M-superfamily, the most notable are the u-conotoxins, which block voltage-gated sodium channels. There are also ••conotoxins, noncompetitive antagonists of the nicotinic acetylcholine receptor.

At the present time, the O-superfamily appears most diverse in terms of the pharmacological function. Family members include ••conotoxins, which block voltage sensitive calcium channels, ••conotoxins that delay the inactivation of voltage sensitive sodium channels, u0-conotoxins which block voltage gated sodium channels and k-conotoxins which block voltage gated potassium channels. In addition, there are
conus peptides with one or no disulfide linkage possess novel pharmacological properties and are significant medical interest (McIntosh, et.al, 2001).

Furthermore, other experts remark conotoxins are paralytic poisons from Pacific cone snails that block the transmission of a nerve impulse from the nerve to the muscle at the neuromuscular junction. There are findings that suggest that the venom of some species contains up to 90 different peptides, small protein fragments that exhibit powerful and highly selective activity on nerves. Moreover, researchers stand to continually be amazed at how the venom seems to change its peptide composition on a whim. Researchers have stated that on a day-to-day basis the proportions of the peptide changes and new compounds appear while others disappear from the venom. However, this newfound painkiller that consists of tiny peptide molecules have intense specific effects on a wide range of molecular targets in nerve cells (O’Neil, 1996).

Individual conotoxins, even within the same class can vary greatly in lethality. Some of the tremors inducing omega conotoxins are not lethal, whereas others of the same group are lethal at low levels. In regards to the toxicity of the complex mixture of peptides that is cone snail venom may be much greater than the sum of its parts due to the synergistic interaction between toxins acting on different aspects of neural function. The chemical properties of conotoxins are reported to be short in peptides of 15-40 amino acids held in very tight conformations by multiple disulfide bridges. These patterns of disulfide bridge help define a number of structural classes of conotoxins. Furthermore, the first Conus peptide for which a complete amino acid sequence was established, and subsequently confirmed by chemical synthesis, was conotoxin GI, a 13-amino acid peptide with two disulfide bonds from Conus geographus venom. This was followed by the characterization of the u-conotoxins, the other major group of paralytic peptides that affect mammals. The presence of these two peptides in the venom of conus geographus explained why stings of this snail are so deadly. With both a potent nicotinic antagonist as well as the sodium channel blocker a toxinological rational could be made for the high fatality rate of humans that are stung (Olivera & Cruz, 2001).

The sites of action of conotoxins are reported to be as follows. At the alpha site are the nicotinic acetylcholine receptors. The effect is a paralysis, which is similar to that seen with curare. Opioid Mu receptor occupation influences the opening and closing of sodium channels. This is also the target for saxitoxin and tetrodotoxin and the effects are also similar. Omega is found at the calcium channels associated with the nerve impulse transmission at the neuromuscular junction. Delta is also at the sodium channels, unlike the mu conotoxins; they slow the inactivation of the sodium channel. Kappa is at the potassium channels. They are also known as shaker peptides because they block a potassium channel known as the shaker and as a result they induce tremors. Lastly, there is the conatonkins found at NMDA glutamate receptors. This blocks nerve impulses that use glutamic acid rather than acetylcholine as the neurotransmitter.

As the findings begin to unravel, conotoxins are very complex group of peptides with over two thousand variants known in the six structural classes identified. Individual members
can be extremely specific for individual subtypes, of which there can be many, of the target molecule. The toxicity of the venom may come less from the considerable toxicity of a limited number of peptides than from the additive or synergistic effects of several toxins acting on different sites.

In addition to the vast and explosive interest in conotoxins as being used as a pain management treatment, the conotoxin has also been viewed as a tool for gaining greater understanding of the electrical excitability of the cells. One study conducted on conotoxins focused on the identification and characterization of pharmacologically active substances, which interact with ion channels. Ion channels are proteins, which are embedded in the outer membrane of nearly all cells of an organism. They mediate the fast, selective transport of ions through the membrane and they are important for many diverse functions in a cell. Voltage gated ion channels are key molecules for the generation of electrical signals in muscle cells and neurons. As a result of the increasing number of voltage activated channels have been identified where mutations of these proteins are the basis for pathological disorders like epilepsy, deafness, or heart arrhythmia. Moreover, during the evolution of different venomous organisms have evolved specific ligands interacting with ion channels have been identified from the cone snail. Conotoxins are a very interesting tool for the investigation of the structure and the function of different ion channels. Conotoxins are small and usually cysteine rich peptides, which have been grouped into several families according to the molecules, they are interacting with.

Toxins affecting voltage gated ion channels have been indispensable not only for the investigation of the physiological function but also for the investigation of the structure of these proteins. The pharmacological properties of the conotoxins identified so far show that these peptides usually exhibit the following characteristics: Conotoxins are highly specific, unusually potent and extremely diverse.

Ziconotide, the generic name, developed from conotoxin, is the United States adopted name (USAN) for the synthetic omega-conopeptide MVIIA, formerly known SNX 111 (Neurex syntheic compound 111). This and related omega-conopeptides are highly basic peptides of about 25-38 residues that have a consistent pattern of six cysteine residues. Ziconotide, and the omega-conopeptides GVIA (SNX - 124) and TVIA (SNX - 185) are selective for the N type calcium channels, whereas others, such as MVIIC (SNX - 230) are broader in specificity (Science Direct, 2003).

Ziconotide is in the late stages of clinical trials as an effective analgesic for chronic pain. An understanding of the factors that control the bioavailability of Ziconotide in the nervous tissue has potential importance for its clinical application. The study conducted detected significant differences in the clearance from the brain after intravenous injection of Ziconotide as compared to SNX - 185. These peptides have distinct sequences, but similar selectivity for calcium channels. Differences in sensitivity to digestion by proteases may explain the differences in clearance rates of SNX - 185 as compared to Ziconotide after intravenous injection (Science Direct, 2003).
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What takes place when pain occurs? Nerves are activated by the influx of calcium ions to the cell’s interior, which in turn triggers the release of compounds that transmit signals between nerves, including the signals that carry pain. The SNX-111 conotoxin molecule is just the right size and shape to block the tiny pores in the nerve cell’s membrane through which the calcium channels blocked, the nerve can not transmit pain signals and the patient is relieved of pain. Due to the fact that most patients with intractable pain eventually become tolerant of powerful opiate drugs such as morphine and pethidine, even when doses were administered at extended ceiling indexes; 1000 times higher than those that would kill a normal person (O’Neil, 1996). The SNX-111 is found to be not only more effective, it appears to have less contingencies than other drugs that might be used in replace of it for instance, morphine or pethidine.

In a study that was conducted SNX-111 infused was directly injected into the spine of seven volunteer patients who had suffered chronic pain for more than 35 years after amputation of nerve damage. The experiment provided the volunteer patients with a tiny pump that delivered a constant dose of the drug. After three days, five of the seven patients reported their pain had disappeared. Of course like any drug there are reported side effects. The side effects from SNX-111 were mild eye jitters, and a slight drop in blood pressure. These side effects are significantly mild compared to the reported side effects of heavy opiate dosages. Normally the side effects from the heavy opiate dosages are lethargic in addition to suffering from impaired intellectual functioning as well as the numerous others (O’Neil, 1996).

Other studies conducted with the use of conotoxins have explored using conotoxins as a treatment of nicotine addiction. A study conducted at the University of Melbourne, acknowledged that nicotine is the key component in cigarette smoking addiction as well as the withdrawal symptoms upon quitting. However, there is little known about the cellular mechanisms underlying these processes. Additionally, findings revealed that neurotoxins as modulators of nicotinic receptor function and neurotransmitter secretion. Investigation of the natural products from the marine world, such as cone snails are being examined as sources of nicotinic receptor blockers and to make derivatives of these that will be more potent and more selective in actions. Other research within the same scope of marine life however, including more species such as sponges, soft corals and the cone snail, which are similar in compounds have been under study in hopes to combat neuropathic pain, schizophrenia, epilepsy, Parkinson’s, and Alzheimer’s disease as well. One of the overall goals of Livett’s (2003) research is to determine the gene sequences of the conotoxins to predict corresponding peptide toxin sequences that can be chemically synthesized and tested for their effects upon the ion channel function in a range of biological assays.

Historically, opiates have been commonly used to treat and manage pain even when the use of opiates is not always appropriate. There are many drugs that offer pain relief that are non-opiates but are not necessarily the first choice. Opioids have been around for hundreds of years. It has been accepted for decades that opioid
analgesics are the mainstay approach for both acute pain and chronic pain relief. Opioids induce analgesia, which is the relieving of pain. It causes drowsiness, the presence of lethargy and sleepiness and changes in mood, which is an individual’s emotional perception. It has been reported to have excellent analgesic and euphoric effects, which in essence are what it attempts to captivate in order to reduce pain.

Administration of opioids to alleviate moderate to severe, acute pain, and chronic pain such as pain endured by cancer patients is considered to be an established management process. That is clinicians need to monitor patients closely and titrate the dose when pain management effectiveness is not achieved, much of this is purely a dangerous guessing game. Although, dose specify is not always easily achieved in patients with chronic pain, advancements in the clinical pharmacological research have shown that opioids are also effective in chronic noncancerous pain which could potentially be less challenging for clinicians. However, the fluxation of doses in pain medicine is problematic for the clinician but also for the patient in pain. Moreover, with the continued use of opioid medication eventually leads to additional problems. For instance, the development of tolerance and subsequently physical dependence. The issue then becomes one that has questionable consequences. Many experts may argue tolerance and physical dependence may not necessarily be harmful to the patient and may not cause the patient to have an addiction while other experts may argue the opposite; suggesting that this type of treatment may be setting the patient up for more at risk resolutions to manage the pain. Moreover, for many patients that have been on opioid therapy for months or years, the analgesic effectiveness tragically becomes less (Goldstein, 2002).

Another source of pain management treatment has been the combination or adjuvant of opioids with nonanalgesics. This area of therapy has advanced enormously in development. Partly because the data has revealed the harmful effects that pure, continued opiate therapies are not effective and lead to other medical problems. Currently, there are many different classes of drugs that can serve as effective adjuvant to opioids for the treatment of pain. More specifically, adjuvant analgesics can be grouped into four major classes according to their use. For instance, drugs that can potentially work for any kind of pain are classified as multipurpose analgesics. Some drugs are specifically used for neuropathic pain, while others are used primarily for musculoskeletal pain, and finally, others are used exclusively for patients with cancer pain (Portenoy, 2000). Findings have revealed that adding adjuvantive medication to opioid therapy improves pain management primarily by nonopioid mechanisms of action. Some of the adjuvants that are used in conjunction with opioids are acetaminophen, antiarrhythmics, anticonvulsants, antidepressants, antipsychotics, baclofen, benzodiazepines, capsaicin, calcium channel blockers, clonidine hydrochloride, central nervous system stimulants, corticosteroids, local anesthetics, N-methyl-D-aspartate receptor antagonist, nonsteroidal anti-inflammatory drugs, pentoxifylline, and scopolamine. Some of the adjuvants are routinely used whereas others such as the
calcium channel blockers are used on a limited basis but offer great potential for broader application (Goldstein, 2002).

Among the multipurpose analgesics are antidepressants, adrenergic agonists, and corticosteroids. The importance of antidepressant analgesia has been recognized for decades. These widely used drugs can potentially help chronic pain of any type. This drug therapy choice is largely dependant on clinical judgments based on careful evaluation of the patient. This can be potentially harmful for the patient, having uncertainty of whether the therapy will be effective, if at all even tolerated will not be ascertained until the drug is already tested by the patient (Portenoy, 2000). Drugs for neuropathic pain are also antidepressant drugs and adrenergic agonist. There have been a large number of drugs that have been targeted specifically for neuropathic pain.

The most popular drug by far for neuropathic pain is gabapentin otherwise known as Neurontin, an anticonvulsant. This drug is very often used to manage pain endured by diabetic patients with polyneuropathy. Additionally, other anticonvulsant medications used in patients with refractory neuropathic pain have demonstrated remarkable results in addition to how vast and quickly the area of adjuvants analgesics is evolving (Portenoy, 2000).

While the anticonvulsant drug family has revealed to be beneficial there is little evidence that supports effective drugs for musculoskeletal pain. Some of the most popular muscle relaxant drugs like orphenadrine (Norflex), methocarbamol (Robaxin), carisoprodol (Soma), chlorzoxazone (Parafen Forte), cyclobenzaprine (Flexeril) or metaxalone (Skelaxin) actually relax skeletal muscle. Moreover, evidence suggests that these drugs are only found to be effective in acute cases of musculoskeletal pain. Although, these muscle relaxants fail to be an excellent drug of choice for arresting musculoskeletal pain they are however effective analgesics. Their sedative and anticholinergic side effects are usually well tolerated, particularly with acute doses (Portenoy, 2000).

According to Goldstein (2002) he states that not only from the perspective of attempting to treat patients in pain, it is vital to do so effectively as well as efficiently. Without the relief of pain patients are at risk of becoming what he refers to as suicidogen, a factor that causes a patient to want to commit suicide.

Moreover, in the current field of clinical pharmacology, the different classes of adjuvantive drugs have been recognized to serve effectively in the management of pain. Adjuvants to opioids are drugs that use specific analgesics, which enhance pain relief primarily through nonopioid mechanisms of action. Examples of adjuvatives are acetaminophen, which is routinely used whereas others, such as nifedpine, a calcium channel blocker, is used on a limited basis but have great potential for more widespread of an application (Goldstein, 2002).

What research has shown is that with the proper use of adjuvants, there is a significant improvement of the analgesia. Additionally, it even offers the potential to lower the dosage and attenuate the opioid induced adverse reactions such as the nausea, vomiting, constipation, pruritus, sedation, and respiratory depression. However, the dose balance that needs to
occur has to be approved by the Food and Drug Administration. Further investigation need to take place in regards to proper dosages. The problem is that the patients are still in pain while in the waiting game for pain relief and or are at risk of harming themselves because the self medicate, ignoring the recommended dosage.

Very often nonsteroidal anti-inflammatory drugs (NSAIDs) remain underused as a medication for pain management especially in cases where opioids are currently being administered. The mechanism of the NSAIDs is to inhibit both the peripheral and central cyclooxygenase. While this serves as a purposeful function the advancements in this type of therapy are in no comparison to the advancements in other related therapies. There are two main forms of NSAIDs, including cyclooxygenase: COX-1, which constitutive, that is, the compounds produced by the activity of this enzyme are necessary for normal physiologic function of stomach, kidney, and platelets. The other is COX-2, which is inducible and involved in inflammation.

It has been recognized that the possibility of selectively inhibited COX-2, while leaving COX-1 uninhibited may produce an NSAID with a greater therapeutic index. Non-selective Cox inhibitors have been available for many years and now include numerous drugs in diverse classes: salicylates, propioic acids, acetic acids, oxicams, naphthylalkaones, and fenamates. The relative selectivity between COX-1 and COX-2 varies across these agents, and drug specific differences in toxicity are partly based on this relative selectivity. Moreover, the advent of highly selective COX-2 inhibitors, for instance celecoxib other wise known as Celebrex and rofecoxib, better known as Vioxx have generated great excitement because of the possibility that these highly selective COX-2 inhibitors will actually be much safer than nonselective COX inhibitors, even those that are more selective for COX-2 than for COX-1 (Portenoy, 2000). However, this attempt to reduce immediate pain has side effect too that at times can be un tolerable.

Additionally, NSAIDs have dose dependent effects. The ceiling dose for analgesic and anti-inflammatory effects has been evaluated in broad terms in dose ranging studies, but, in any individual patient, the minimum effective dose and ceiling dose are unknown, suggesting the value of dose titration. All these drugs are nonspecific analgesics and can be effective for a variety of pain syndromes. Additionally, they produce no physical dependence or tolerance, a positive note. Even though there are much more clinically reported positive results from such selective treatment, there are, like most drug therapies significant side effects. Part of the draw back in choosing NSAIDs is the selection in dosing; it is truly based on best clinical judgment. With this in mind, very often physicians generally titrate from a low dose and increase if warranted. The need to recognize the ceiling effects is essential as well as vital because most of the adverse effects are occult. For instance, massive GI hemorrhage increase with dose, but one cannot predict that risk. Very often these adverse effects present with a life threatening hemorrhage. Moreover, it is necessary that clinicians recognize the high-risk patients for example, the elderly, those receiving corticosteroids or anticoagulants, and those who have previously experienced NSAIDs toxicity. Furthermore,
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Clinicians are faced with searching out the safest agents possible with the least amount of adverse effects as well as the minimal effective dose (Portenoy, 2000).

Other potential hazards are drugs that are available over the counter (OTC) are not correctly being used or taken, often overused which can result in non-effective pain management in addition to the general public believing that prescription medication is more potent which suggests that OTC medications must then be less effective.

According to new data released by the National Consumers League (NCL), the ongoing abuse and misuse of OTC, pain relievers such as ibuprofen and naproxen is a very real problem in the United States. A survey of 4,263 adults revealed that more than 175 million adult Americans take OTC medications for pain relief, and many of them are doing it without regard for their safety. The statistics revealed that 84% of the population is practicing these harmful behaviors. Forty-four percent admitted to exceeding the recommended dose and a large number of people ignore the critical label information. For instance, it is recommended that if you are taking certain OTC’s that you not consume alcohol, and even certain prescriptions as well. NCL released the survey to help educate the 30 million consumers who take NSAIDs about the possible dangers of improper use. The NCL reported that they were disheartened by what the results revealed. They stated that it is obvious and now supported by the data that consumer’s just want the pain to go away so they take more medication then what is instructed; putting themselves at risk without realizing the potential harm they may ensue.

Statistics show that 16,500 people die each year, and 103,000 are hospitalized from NSAIDs related complications. Additionally, the use of OTC NSAIDs increases the risk of stomach bleeding by two or three times and most serious side effects can occur without warning symptoms. OTC painkillers bring relief to millions of Americans for arthritis, headaches, and other common pains. But these drugs, while convenient are not foolproof and could result in hospitalization. Furthermore, many people overlook the risks of mixing the OTC’s with other medications, especially cold remedies with multiple active ingredients, prescription drugs, and alcohol. Any one of these combinations can be harmful, even deadly. Additionally, the study yielded findings that stated almost half of the participants were more interested in having pain relief than the possible risks (Griffin, 2003).

The focus of this issue is not specifically on drug treatment preference rather it is to have pharmacological drug choices that are highly selective in the way it eradicates pain with little to no side effects and overall suggested to be the safest it taken properly. Any professional treating patients with unresolved pain clearly recognizes the importance to effectively and immediately improve the pain-inflicted patients overall quality of life. It is for these reasons among others that continual research in the area of pharmacological pain management needs to propel forward. There are several different pharmacological paths that one can follow for pain management. However, pain management has been revealed to be a slippery slope. Although it might appear to be an easy task with so many medical options, research has clearly indicated
that treating pain is no simple matter in addition to the many and potentially dangerous risks that are taken or ensued. When traditional pain treatments fail what is the next alternative treatment? Some choose therapies that are out of the ordinary scope of traditional medical treatments.

Research has revealed already the therapeutic use of Bee venom, also known as Apitherapy. The medicinal use of honeybee products has been practiced since ancient times. In the modern world of honey bee venom has found wide uses in treating arthritis and other inflammatory and degenerative diseases. The world scientific literature contains more than 1500 articles on bee venom. Honeybee venom contains at least 18 active substances. Melittin, the most prevalent substance in the honeybee venom, is one of the most potent anti-inflammatory agents known. Reported to be 100 times more potent than hydrocortisol. Bee venom has been reported to be useful in the treatment of arthritis and other systemic inflammations, acute and chronic injuries, scar tissue, and multiple sclerosis. Although this form of treatment has significant therapeutic benefits it has a significant draw back. In order to receive bee venom treatment to relieve pain one must become stung by the venomous bees Whole Health (2001).

Although there is no data that suggests that this type of treatment may cause more pain or induce more pain than originally felt, it feels like it would. Moreover, bee venom treatment has indicated to have many positive effects, the draw backs are not only finding a beekeeper that can assist in the implementation of treatment but a patient that has possibly exhausted all other treatment options and can handle the stinging process. This form of pain management is difficult to determine how effective it truly is as a pain management treatment. This treatment is not marked or tracked by pharmaceutical companies or physicians. Data gathered in this area is likely to be limited and possibly unreported. In essence, this form of pain management therapy is very contained.

Other natural species have been examined and discovered to have medicinal properties for the treatment of pain, for instance, Epipedobates, a type of frog. Within the rainforest of Ecuador resides a small, colorful, seemingly harmless amphibian called Epipedobates tricolor. This frog first introduced itself to the scientific world in 1974. Epibatidine is an alkaloid (nitrogen containing) compound that was isolated from the skin of Epipedobates tricolor frog. The initial alkaloid was called 208/210. Epibatidine has been found to be a potent analgesic but has some deleterious side effects such as paralysis. This potent analgesic was found to be 200 times more potent than morphine and the mechanism of action appeared to be non-opioid. It has an affinity for the nicotine receptor in humans. This is unique in that most analgesics modulate the feeling of pain by binding to the opiate receptors. The drawback to opiate drugs is that they are tremendously addictive (Daly, 1999).

Researchers at Abbott laboratories have recently synthesized an epibatidine analog called ABT-594. This compound seems to have some of the most promise as an analgesic drug. It has very low affinity for nicotine receptors in the neuromuscular junction, which cause the paralysis effect. However, it has high affinity for the nicotine receptors in the central nervous system, which regulate pain perception.
Epibatidine’s interest to the scientific world was in most part for its analgesic properties. ABT-594 exhibits improved ability to block the same range of pain conditions and yet contains none of the ill side effects of morphine. The issue that needs to be determined with this pain management therapy is whether or not it has addictive traits. Moreover, any scientific findings that are effective in treating pain and have less known side effects is a positive. However, offering drugs that may be as potentially addictive as some of the pain therapies already offered is what researchers what to avoid. Rather, lets not just keep adding ineffective drug therapies to the pile lets only add more effective drugs without side effects.

Developing new forms of pain relievers that are safe and effective for patients with pain while being more addictive resistant formulations is what most researchers are aiming for. Moreover, developing drugs that are abuse - resistant is not only difficult but also almost impossible according to Goldenheim (2003), leading researchers at Purdue Pharmaceuticals as a result of most of the drugs being developed are opioids and or have opiate prosperities. While there are many modalities that can be used in managing pain, drug treatment remains, for the most part, the cornerstone of treatment. Opioids remain in their position as the foundation of most analgesic strategies, it may soon take a back seat as the developing and therapeutic use of conotoxins are more frequently used.

Venom is clearly the major weapon used by cone snails for prey capture. The venom may also be used for the other biological purposes. In many ways, the contents of the venom provide a biochemical reflection of the biotic interactions critical to the success of failure of the species. Consequently, the cone snail has definitively known as the most species-rich of all the marine invertebrate genera. Through this expansion into hundreds of species, basic strategy of the venom remains the same small, structured peptides, derived by the diversification of a few gene superfamilies, potently affecting the nervous systems of potential prey, predators and competitors. Although human are not prey for the cone snails, in the near future cone snail toxins may be used by physicians to deliberately envenomate humans to treat a variety of disease states. Some of the disease targets are already under investigation for treatment by the cone derived toxins include chronic pain, epilepsy, cardiovascular disease, psychiatric disorders, movement disorders, and spasticity, cancer and stroke as well as neuromuscular blocking agents as adjuvants in anesthesia (McIntosh, et.al., 2001).

Discussion

The initial point of this article was to examine the several different ways in which pharmacological treatment approaches have attempted to treat and manage acute and chronic pain. It has been revealed that opiates, what was once considered to be effective pain treatment, may not be where the future of pain management will be. Specifically, venoms, conotoxins to be more direct, appear to be overturning the mainstay in drug treatment. As it was noted, cone snail venom is highly selective and specifically effective in eradicating pain. In addition, conotoxin studies have yielded results that show conotoxin therapies are not addictive, and have tolerable indexes unlike opioids. In
addition, conotoxins side effects are much milder and easier to manage than those of opioids. Conotoxins are considered to be the miracle medicine. Numerous conotoxins have been patented for a variety of medical applications. Over 80 new patents and PCT publications have appeared over the past five years. In essence, because peptides demonstrate greater selectivity than other agents conotoxins are powerful in treatment of pain management. In resent literature an article was published in the magazine Science World. The title of the article was called "Venom: Miracle Medicine." This article was about a girl named Laura McManus, and a rare condition of stress-triggered muscle spasms. Here’s her story:

It was reported that one day when Laura was 14 years old she was outside doing yard work when she fell to the ground with excruciating pain. After going to the hospital Mt. Sinai, New York, the doctors told her of her stress-triggered spasms. Laura’s x-rays showed that Laura had an extra vertebrae lodged at the base of her spine. Under any exertion, the vertebrae would move and squeeze nearby nerves.

Unfortunately, 10 years later Laura was still in constant pain. She had over five operations and was habitually taking painkillers. Her doctors came up with the idea of installing a pump into her spine. The fairly large device would constantly pump painkillers into her nearby nerves. The pump-system idea was a failure because of the persistent dull pain remaining in her back. For the next two years Laura was extremely depressed and still in constant pain. Her mobility was dependent on a cane and at 26 years old she did not want to live her life like this. This story clearly delineates a point that was raised earlier in this article. When a person is in such excruciating pain for a long period of time they tend to have suicidogen thoughts.

After this long drawn out painful journey Laura’s doctor had phoned her one morning and told her about a new experimental drug for pain. The drug is called SNX-111, and it is made from venom of a cone snail. Laura, at this point was skeptical about the venom but at her wits end, and would try anything. The new medicine worked instantly, Laura was amazed, the drug had worked, it saved her life (personal communication, February 10, 2003).

Moreover, the goal of this article was to bring to the surface not only the vital importance of conotoxins but also how this literature needs to reach out and be reviewed by the masses. The research and conotoxin experts significantly revealed that venoms would be the new cornerstones, replacing opiates, in drug therapies for pain management. With Ziconotide already in clinical trials as effective analgesic for chronic pain, the use of cone snail venoms further supports the growing importance of conotoxin exploration as a pain management therapy.

As noted by Kaplan and Sadock (1998) when understanding the concept of pain it is important to recognize that pain may be serving as a simultaneous symptom of psychological stress or even a defense against it. It is vital that more exploration in the area of pain management a psychological occurrences be conducted. These finding could yield results that suggest any individual who suffers from persistent to chronic pain receive psychological support in addition to their pain management therapy.

Furthermore, the only current limitation to conotoxins is not
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unlike any new drug that is being explored to pharmacological purposes; it take years of clinical trials in addition to FDA approval before it hits the market and can be offered to the pain suffering individuals. Moreover, there are mild side effects; it is non-addictive, and less abrasive on the overall body. This wonder from the sea presents a potential drug to reduce the pain and suffering for thousands of people afflicted with chronic pain.

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