Methadone Related Deaths (MRD) Among
Complex Regional Pain Syndrome (CRPS) Patients

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Abstract: From 1995-2002 we documented 10 patients suffering from complex regional pain syndrome (CRPS) who died as a result of methadone toxicity (MT). Methadone Related Deaths (MRD) has been recognized for decades. It has become a "global epidemic" for many chronic pain patients, including CRPS patients, and patients suffering from drug dependency. We have been in personal contact with 10 CRPS families who have lost loved ones due to MT, which can cause respiratory failure. Three out of the 10 CRPS patients that had died, were waiting to come to our clinic as new patients. It is sad to think that the doctors treating these patients thought that they were helping their patients and the patient thought that they were on the proper medication to treat their CRPS pain. The only thing that methadone did for these patients was cause them an early death. We are left to wonder how many other patients have died as a result of taking methadone that we are unaware of.

In this article we will discuss the reasons why methadone use is not appropriate for the treatment of CRPS. We will also discuss the overall dangers and cautions of methadone generally.

Key words: *Complex Regional Pain Syndrome (CRPS), Methadone, Methadone Related Deaths (MRD), Methadone Maintenance Treatment (MMT), Methadone Toxicity (MT), Reflex Sympathetic Dystrophy (RSD).*

INTRODUCTION

Historically, methadone (amidon) has been used as an alternative form of treatment for heroin addicts; as a harm reduction strategy. The use of methadone does not cure the heroin addiction; instead it is used as an opioid substitution therapy (1-4). Despite this, methadone is preferable because it has a longer half-life lasting in the system for over 24 to 48 hours (5, 6). Therefore, the patient does not develop a sharp withdrawal (rebound) as the patient experiences with the use of heroin. Methadone has also been used for decades to help treat chronic pain patients (3, 4).

For more than a century, complex regional pain syndrome (CRPS) also known as reflex sympathetic dystrophy (RSD) has been recognized as a syndrome (7-10). This syndrome is a complex form of neuropathic pain associated with hyperpathia; neurovascular instability, neuroinflammation, and limbic system dysfunction (7, 11). It is triggered by stimulation of neurovascular thermoreceptor c-fibers sensitized to norepinephrine. This afferent sensory impulse leads to CRPS. The syndrome involves extremities, head, back, shoulder, breast, as well as viscera (7, 11).

The use of opioids plays a major role in the control of pain and inflammation in the peripheral and central nervous system (12). The endogenous ligands-opioid peptides (endorphins) are expressed by resident immune cells in peripheral tissues (12).

Depriving the patient of proper pain medication can aggravate the immune system dysfunction. The selection of proper opiates for treatment of CRPS is quite critical.

Both opioid agonists and mixed morphine agonist-antagonists have been used for treatment of pain in such patients (7).

Opiates are considered effective in the treatment of neuropathic pain (13). However, due to the complexity and multiple origins of the pain in CRPS, in some patients the opioid agonists are not as effective (7, 14). The effectiveness of methadone for pain relief only last for 4-6 hours (1).

Since the 1990's methadone has also been used to treat cancer pain and other forms of chronic pain conditions such as CRPS.

Methadone treatment should be limited to cancer pain patients who have a short life expectancy. Unfortunately, over the years, there has been much confusion with mixing different forms of cancer pain treatment and applying it to the treatment of CRPS patients.

COMPLEX REGIONAL PAIN SYNDROME (CRPS)

In January of 1994, Merskey and Bogduk defined complex regional pain syndrome (CRPS) as the following classification: CRPS Type I (RSD) is a syndrome that usually develops after an initiating noxious event, is not limited to the distribution of a single peripheral nerve, and is apparently disproportionate to the inciting event. It is associated at some point with evidence of changes in skin blood-flow, edema, abnormal sudomotor activity (sweating) in the region of the pain, or allodynia or hyperalgesia (15). "The symptoms and signs may spread proximally or involve other extremities and internal organs (11). Impairment of motor function is frequently seen (15)." They clarify associated symptoms and signs and specify "atrophy of the skin, nails, and other tissues, alterations in hair growth, and loss of joint mobility may develop. Guarding of the affected extremity is usually observed (15)."

The other form of CRPS, CRPS Type II (causalgia), which refers to the causalgic form of RSD, points to the fact that in causalgia there is ectopic and ephaptic nerve damage bypassing the synaptic transmission of electric current in nerve fibers between the adjacent damaged smaller and larger myelinated nerves (16-23).

The term CRPS II is more specific than causalgia, which is nonspecific and can be present in conditions other than CRPS (22, 23).

This is a long but relatively comprehensive definition of CRPS. Building on the basis of this comprehensive definition of CRPS, one can come to the conclusion that CRPS is a syndrome with multiple manifestations which require the following minimal symptoms and signs for the condition to be called CRPS.

1. Pain: constant, burning pain, and in some forms at times during the course of the disease, stabbing type of pain (causalgic). The pain is relentless and is invariably accompanied by allodynia (even simple touch or breeze aggravating the pain) and hyperpathia (marked painful response to the simplest stimulation).

2. Spasms in the blood vessels of the skin and muscles of the extremities are a result of the extremity being cold. These muscle spasms result in tremors, and movement disorder such as dystonia, flexion spasm, weakness, clumsiness of the extremities, and tendency to fall.

3. CRPS is accompanied by a certain degree of inflammation in practically all cases. This inflammation may be in the form of swelling (edema), skin rash (neurodermatitis), inflammatory changes of the skin color (mottled or purplish, bluish or reddish or pale discolorations), the tendency for bleeding in the skin, skin becoming easily bruised, inflammation and swelling around the joints as well as in the joints (such as wrists, shoulders, knee, etc.) which can be identified on MRI in later stages, and secondary freezing of the joints.

4. The fourth component and prerequisite for the diagnosis of CRPS are insomnia and emotional disturbance. The fact that the sympathetic sensory nerve fibers carry the sympathetic pain and impulse up to the brain which terminates in the part of the brain called the "limbic system." This limbic (marginal) system which is positioned between the old brain (brainstem) and the new brain (cerebral hemispheres) is mainly located over the temporal and frontal lobes of the brain. The disturbance of function of these parts of the brain results in insomnia, agitation, depression, irritability, and disturbance of judgment. Insomnia is an integral part of an untreated CRPS. So are problems of depression, irritability and agitation.

The clinical diagnosis of CRPS is based on the above four principles which help confirm the diagnosis of the disease. Simply knowing the existence of CRPS in a region is not enough. The four principles do not accurately localize the area of nerve damage/dysfunction, and it does not differentiate the original source of pain. This information is essential to help the clinician avoid causing more damage by performing surgery, or inserting a needle in the area containing already permanently damaged neurosensory nerves.

Once the patient meets the above four criteria (which may be present in different degrees and different severity), the diagnosis of CRPS can be established.

DIAGNOSTIC CRITERIA

In our study of 824 CRPS patients revealed the fact that a complex syndrome such as CRPS cannot be expected to be diagnosed with a single laboratory test such as triphasic bone scan (TBS), infrared thermal imaging (ITI), and quantitative sudomotor response test (QSART) (7).

A standard diagnostic criteria needs to be implemented when diagnosing CRPS (Table I).

The following diagnostic tools should be used to help ensure a proper diagnosis of CRPS:

- Taking a careful history of the patients signs and symptoms
- Physical examination
- Triphasic bone scan (TBS)
- Infrared thermal imaging (ITI)
- Diagnostic nerve blocks
- Laser Evoked Potential (LEP)
- Quantitative thermal sensory evoked response test (QST)
- Quantitative sudomotor response test (QSART)

It is most important that CRPS patients receive an early diagnosis, along with early treatment, early physical therapy, and the use of nerve blocks, as well as detoxification from harmful medications which will help give the patient a better quality of life.

Also, it is imperative to spare the patient from any unnecessary surgical procedures that can cause more pain and spread of CRPS (7, 11).

As a result, in CRPS, most patients invariably suffer from limbic system dysfunction such as insomnia, agitation, irritability, depression, poor memory, and poor judgment (7) (Table I).

The diagnosis of CRPS is a clinical one, on the basis of the four standard diagnostic criteria outlined in (Table I).

Table I. Diagnostic Criteria for the Clinical Diagnosis of CRPS

The following four criteria's are necessary for diagnosis of CRPS (7).

1. Neuropathic pain in the form of: ▪ Allodynic and hyperpathic pain elicited by simple stimuli that do not usually cause pain such as touch or breeze, and an exaggerated regional pain after simple stimulation. ▪ Hyperpathic pain: Increased sensitivity to touch (with objective sign of changes in sweating and rapid pulse in response to pain stimulation) with a tendency for secondary regional spread to the adjacent areas of the limb.	2. A motor response to the sensory stimulation. ▪ Vasomotor (color and temperature changes of the extremity) ▪ Motor dysfunction (flexion deformity, muscle spasm, dystonia or tremor).
3. Inflammation ▪ Swelling of the extremity ▪ Neurodermatitis ▪ Spontaneous bruising ▪ Swelling causing entrapment mimicking carpal tunnel, tarsal tunnel, or thoracic outlet syndrome.	4. Limbic system dysfunction* ▪ Insomnia ▪ Irritability and agitation ▪ Poor memory ▪ Depression ▪ Poor judgment

*The fourth principle, the disturbance of the limbic system function (the marginal part of the brain responsible for mood, memory, and judgment), is essential for definitive diagnosis of CRPS (7).

HISTORY OF METHADONE

In 1937 the synthetic opiate Methadone (Hoechst-10820) also known as Polamidon was developed at the I.G. Farbenindustrie Pharmaceutical Laboratories by two German scientists, Bockmühl and Ehrhart during World War II to help treat German soldiers who were addicted to opium (1, 2). In September of 1941 Bockmühl and Ehrhart had filed for a patent for their discovery. After World War II, the United States had obtained the rights to this drug from war requisitions. In 1947 methadone was introduced in the United States by Eli Lilly and Company to help control pain and drug addiction (3, 4).

The research work done by Isbell and colleagues in 1947, showed that methadone caused signs of toxicity, inflammation of the skin, deep narcosis, and general appearance of illness (24). They also believe that methadone had a high potential for addiction (24).

Also, in 1947 the FDA approved the use of methadone as an analgesic to treat pain. By 1950, methadone was being used to treat the withdrawal symptoms of heroin and other addictive opioids.

In 1964, Dole and Nyswander from Rockefeller University in New York conducted experiments using methadone to treat heroin addicts. In 1965, they published an article in JAMA reporting that they had success in treating 22 addicts with methadone (25). By 1966, the number of drug addicts that they were treating with methadone increased to 750 (26). This form of treatment for drug addicts would become known as methadone maintenance treatment (MMT).

Methadone is classified as a schedule II controlled substance. Under the approved narcotic addiction programs within the FDA, the use of methadone was limited to "detoxification treatment" or "maintenance treatment" (27). In 1976 this restriction was removed allowing physicians with appropriate DEA registration to prescribe methadone as an analgesic for such conditions as chronic pain (28, 29).

Inturissi and Verebely both report that the residence time of methadone is very long. The pharmacokinetic half-lives of methadone disappearance rang is from 15-30 hours (30).

Over the past few decades methadone has become an overly prescribed medication due to the fact that it is less expensive (for the insurance companies) than other opioids that are prescribed to treat chronic pain and drug addiction(31-33).

METHADONE RELATED DEATHS (MRD)

Methadone Related Deaths (MRD) have been widely reported globally from the United States, Australia, Canada, China, England, Germany, New Zealand, and throughout Europe.

In the late 1940s, clinical trials of methadone were implicated in the death of one patient and for causing severe respiratory depression in another.

In the 1950s, several deaths of children were reported in England and Germany as a result of exposure to methadone, which was typically found in cough syrups (34). Other deaths were reported in many other countries where methadone was widely used (34).

Segal and Catherman reported from 1967-1969 that there were only four related deaths to methadone (35). The number increased in 1970 to 22, in 1971 it rose to 27, and in the first 10 months of 1972 it rose to 37(35).

Of the deaths in 1972, 17 were directly attributable to methadone, 15 were attributable to a combination of methadone and one or more other narcotic and dangerous drugs, and five were due to causes other than drugs but methadone was found by postmortem toxicology. An additional 15 deaths related to methadone occurred in the last two months of 1972 bringing the total to 52 cases.

Among the additional deaths, 10 were directly attributable to methadone and four to a combination of methadone and one or more other narcotic and dangerous drugs. One was most likely a suicide following ingestion of methadone and other sedative medications (35).

Drummer et al. reported 10 deaths within days after the patients started MMT. The cause of death was methadone toxicity in combination with bronchopneumonia (5).

According to the Centers for Disease Control and Prevention (CDC) they reported that from 1999-2004 there were 12,413 MRD in the United States (36).

The CDC also reports that methadone represents only about 2% of opioid prescriptions written but is associated with one-third of drug related deaths are from methadone use (36).

According to data from the National Center for Health Statistics, from 1999 to 2005 methadone-related poisoning deaths increased by 468 percent, while total poisoning deaths increased by only 66 percent (37).

In addition, methadone-related poisoning deaths had the greatest percentage increase of deaths compared with other opioids (37).

The CDC also reported that by 2009, MRD had risen six-fold over the previous decade (38). During that same year, nearly 4 million methadone prescriptions were written for pain (38).

According to a 2014 CDC study by Chen at al. reported that death involving methadone among drug dependency and chronic pain patients has increased from 784 deaths in 1999 to 4,518 deaths in 2007(39).

Between the years 1993-2004 there were a total of 3,298 deaths involving methadone reported in England and Wales (40).

From 2004-2010 Cao et al. performed a six year cohort study on 1,511 MMT patients in China (41). Out of the 1,511 patients in the study 154 patients had died from MRD (41).

In a 2015 study by Ray et al. showed the risk of out-of-hospital deaths among non-cancer pain patients who were treated with methadone was 46% greater than patients taking morphine (SR) sustained-released tablet. Deaths were reported even when the patient was taking a dose as low as 20 mg/d. (42). Their findings show that methadone should not be the first choice of treatment for non-cancer pain patients (42).

The latest methadone epidemic related to accidental deaths of toddlers and young children. There have been many cases reported in the U.S., Australia, England, and throughout Europe over the past few years (43). These children had been given methadone to help keep them quiet and to help them sleep. Some of these deaths were accidental and some were intentional by the child's parents or caregivers (34, 43-46).

In a study by Milroy and Forrest, analyzed 111 cases of methadone poising were examined (46). Out of these 111 cases, methadone was the sole cause of death in 55 of the cases. Five out of the 55 MRD were children under the age of 14 (46).

In another study from NSW Australia, Nielssen et al. reported that five children had died from a methadone overdose (43). It is evident that over the past few decades, the number of MRD has increased globally on a yearly basis; there is significant cause for concern.

IS METHADONE TREATMENT SAFE?

In our view chronic pain has been treated for decades by a Freudian type of psychiatrists. The psychiatrist would convince the patient that, according to the teachings of Freud, the patient had a sick personality, the pain was imaginary and it was all in their head. Even in the 1960's and 1970's there were all types of Freudian archaic theories such as "pain personality," "multiple sclerosis personality," or "Münchausen Syndrome." The psychiatrist believed that the patient was a big liar just as Baron Münchausen of the 16th century. It sounded more scientific when the psychiatrist was projecting and accusing the patient of lying.

Methadone was first introduced to the United States in 1947 to help patients who suffer from drug addiction (e.g., heroin addicts) and chronic pain (3, 4). Methadone was quite impressive because it has a long half-life more than 24-48 hours, and even though the brain becomes dependent on it, the patient does not realize the dependence because the withdrawal effect is very mild (5, 6). In addition, it was quite effective because frequently the heroine addict would take the methadone, and heroine at the same time, this would cause the patient to die of respiratory arrest. The cause of death was then declared as a heroine overdose. This was a convenient way of quietly getting rid of the heroine addicts. In the late 1980's and the early 1990's there was the resurgence of methadone treatment because of the doctors' lack of understanding and dangers of this insidious, strong respiratory depressant opioid agonist. The patients taking methadone have problems with shortness of breath, suddenly falling asleep, having apneic attacks, and death. These attacks are diagnosed as "narcolepsy," and the physician does not recognize the link between the respiratory depression and the methadone.

In our research, methadone is no different from other types of morphine agonists in regard to tendency for physical dependence. The only difference is that methadone has a long half-life, and can last in the system for a few days. In that regard, the rebound phenomenon (withdrawal) is not noticeable when multiple doses of the medicine are prescribed such as in the dose of two or three times a day. By the time the previous day's is practically all out of the system, the second dose replaces it. In this regard, it is very similar to other medications such as ms contin (morphine sulfate controlled-release) or other long duration skin patches such as duragesic patch (fentanyl transdermal system). Clinically, the fact that withdrawal (the rebound phenomenon) is accelerated and is camouflaged by overlapping dosages of the medications, and the adverse effect on the brain is accelerated. This adverse effect consists of practically complete arrest of formation of cerebral endorphins and secondary side effects of reduction of estrogen and other types of hormones related to the hypothalamus of the brain.

As a result, the patient becomes fatigued, has a tendency to gain weight, has a tendency to be inactive, and especially during the night while sleeping the extremities do not have the normal tossing and turning so the inactivity can aggravate CRPS and can aggravate the edema and inflammation that is associated with CRPS. Also such patients show a significant suppression of the brain endo benzodiazepines (endoBZs) and natural cerebral antidepressants.

There are a few safe ways to discontinue such long lasting opiates.

The research work by Ling and Wesson, found the use of buprenorphine (buprenex) to be promising for the treatment of "poly drug" abuse (7, 47). This analgesic medication has been tried on patients dependent on both opiates and Cocaine. Buprenorphine, an opiate agonist-antagonist, is a strong analgesic without causing dysphoria, or dependence (7, 47-49). Sublingual buprenorphine has been used successfully for detoxification from cocaine, heroin and methadone dependence (7, 47-49). Buprenorphine is a Class V narcotic in contrast to morphine, methadone or fentanyl, which are Class II narcotics. In addition, it has been found to have some advantages over methadone in terms of relative safety in the treatment of heroin addiction. Surprisingly, it is also effective in reducing the side effects of cocaine withdrawal.

The greatest researchers and professors who are experts in surgical procedures and in the latest advances in mechanism of diseases know very little about dependency to drugs. It is our belief that the higher quality the university or research center the more likely they are to prescribe morphine agonist narcotics and to try to get rid of the pain with surgical procedures that are doomed to fail.

The best example is the doctors in cancer institutes who advocate the same pain medicines for cancer patients as they do for CRPS patients. The cancer patient has a few months to live, and as a mercy act, should receive any of the strongest pain medicines or any surgical procedure that provides them a few months of pain relief.

CRPS patients have a full life ahead of them despite pain, and should not be exposed to treatments that have adverse effects that are worse than the disease itself.

DETOXIFICATION FROM METHADONE

In our clinic, we have found a helpful form of detoxification from methadone and other opiate agonist's dependence by switching the patient to stadol and ultram in a cold turkey fashion as long as the patient also takes klonopin to reduce any chances of potential for seizure disorder from ultram.

Unfortunately the general trend nowadays is to prescribe patients with all types of strong pain medications instead of providing the appropriate, and adequate care - such as ensuring they are on a proper and safe treatment plan.

Morphine agonist narcotics have very little effect on neuropathic pain such as CRPS. However, insurance companies are providing all the cheap narcotics patients may need instead of putting funding towards any curative treatment which may cost more money. The agonist opioids (such as methadone) are less expensive and they keep the patient quiet in between office visits.

Detoxification should be under-taken on a case-by-case basis. It is unfortunate that the medical community does not discuss in more depth the harms and benefits of treatments such as this; many patients are likely to be on medications such as methadone without fully understanding and consenting to the harms associated with them.

METHADONE AND RESPIRATORY DEPRESSION

There have been many published case reports of methadone causing death. According to Hunt and Bruera, they reported a case of a patient who developed severe sedation, respiratory depression and non-cardiogenic pulmonary edema after several days of treatment with a low equianalgesic dose of oral methadone (50).

The effects of methadone can stay in a patients system for 24-48 hours after taking a single dose (5). Respiratory depression is the main symptom in methadone deaths (51). Caplehorn reported that studies from MMT clinics showed that respiratory depression was the cause of death in Methadone cases (52).

According to Segal and Catherman, reported that individuals who died following the ingestion of methadone may have had a period of up to a few hours where they manifested no ill effects of the drug (35). This was followed by a period of increasing cerebral and respiratory depression and death (35).

In addition to this, a number of other researchers have reported other harms of methadone use including:

- Barrett and colleagues showed that the respiratory-depressant effect of methadone lasts up to 48 hours after a single dose, whereas the analgesic effects last only 4 to 6 hours (6). The residence time of methadone is very long.

- Wolff et al. found in their research that the pharmacokinetic half-live of methadone in healthy subject ranges from 33-46 hours and, it could be longer in patients who use opiates (53).

- Ehert and colleagues reported that a lethal respiratory depressive effect can result from taking a dose as low as 30mg (54).

- Drummer et al. found that methadone toxicity does cause respiratory depression, which predispose the development of bronchopneumonia (5).

- Modesto-Lowe et al. recent research has found that methadone fatalities have been associated with respiratory depression during treatment for patients suffering from drug addiction and it is also seen in patients being treated for chronic pain (55).

- Corkery at al. reported that respiratory depression is the probable mode of death in methadone cases (56).

Methadone has been reported over the years to cause fatal overdoses (5, 57-59). The primary toxic effect of methadone is respiratory depression and hypoxia; it can also cause pulmonary edema and/or aspiration pneumonia (60, 61).

As previously stated, the use of methadone is a potent drug; it must be used under professional care, and be decided as the most effective treatment out of all other options prior to being used. Further, patients must be carefully monitored on an ongoing basis.

METHADONE EDUCATION

There has to be some form of education between the physician and patient regarding the dangers of taking methadone.

The following guidelines should be used to ensure all (CRPS patients, chronic pain patients and drug dependant patients) are treated by qualified professionals who have a strong understanding of methadone use and associated harms and consequences as well, to ensure that patients are well informed about methadone use, and the harms associated:

- Physicians should have a strong understanding and be well trained in prescribing methadone
- Patients blood toxicity levels should be checked frequently(on a weekly or monthly basis depending on the patients case)
- Physicians should discuss the adverse reactions and dangers of taking methadone
- Physicians must monitor the patient and discuss potential drug interactions to other medications that the patient maybe taking
- Discuss the respiratory-depressant effect of methadone
- Discuss the side effects of taking methadone
- Discuss the life-threatening problems(e.g. respiratory depression, heart failure and death) that can be caused by methadone
- Discuss the fact that methadone stays in the patients system longer than any other opioid (24-48 hours)
- Patients should alert their physician of any changes in their health(e.g. shortness of breath, irregular heartbeat, chest pain, narcolepsy, etc.) or other problems while taking methadone and ask any questions that they may have regarding methadone
- Patients should inform all their providers that they are taking methadone
- Discuss a treatment plan to help patients discontinue methadone in a safe manner
- Discuss other safer alternative medication options other than methadone

ADVERSE REACTIONS TO METHADONE

As prior discussed in detail, methadone causes many different adverse reactions such as life-threatening breathing problems, respiratory depression, bronchospasm, hypotension, chest pain, tachycardia, abnormal heart rhythm, heart failure, seizures, and death.

BRAND NAMES OF METHADONE

The following are some of the brand names for methadone: methadose, dolophine, amidone, heptadon, physeptone, and symoron. Methadone is offered in the following forms: pill, liquid, and wafer.

FDA WARNING

On November 27, 2006 the FDA had issued a public health advisory warning regarding methadone. They stated that methadone causes death, narcotic overdose, respiratory depression, and cardiac arrhythmias. They also approved new prescribing information for the use of methadone (62).

MEDICAID PERFERED DRUG LISTS

Since January of 2012, there are 31 states that have methadone on the Medicaid Preferred Drug List (MPDL). There are 18 stated that do not list methadone on their MPDL and there are two states that have no MPDL (Table II).

Table II. State Medicaid Preferred Drug Lists For The Use of Methadone

States that have Methadone on the Medicaid Preferred Drug List	States that do not have Methadone on the Medicaid Preferred Drug List	States with no Preferred Drug List
AL, AK, AZ, CA, CO,CT, DE, FL, HI, IA, ID, IL, IN, KY, LA, MA, MD, ME, MI, MS, NE, NJ, NM, OH, OK, PA, UT, VA, VT, WA, WI.	AR, DC, GA, KS, MO, MN, MT, NC, NH, NY, NV, OR, RI, SC, TN, TX, WV, WY.	ND, SD

CONCLUSION

The medical community has to understand how dangerous the use of methadone can be for CRPS patients, chronic pain patients and for patients, who are trying to recover from drug dependence from heroin, cocaine, morphine, and other addictive drugs.

What is truly unethical in the treatment of CRPS patients and recovering drug addicts is the fact that a combination of methadone and other strong opioids has the potential of causing narcolepsy, respiratory arrest, and death. Just because methadone has a long half- life and causes subtle rebound and dependence does not prove it to be a safe drug. Patients who are on a MMT program should be very careful of any additional medications that they are taking along with methadone. While patients are being treated with methadone, they should have their blood toxicity level checked weekly or if not monthly, to make sure that they are on a safe dose of methadone.

The medical community must be cognizant, and cautious about drug dependency discussions and assumptions. Doctors should understand that not all prescription drug users are drug abusers and addicts; for every one abuser, there are a handful of patients who need it and are not misusing. They should not prescribe drug dependant types of analgesics for pain patients and then be labeling them as drug seekers or addicts. There is a line between drug use and drug abuse/misuse. Drug abuse/misuse among chronic pain patients is a real issue, and must be mitigated by ensuring doctors are closely monitoring their patients for warning signs of dependence and misuse as well as ensuring proper dosing.

Many of these drugs actually make the pain worse in-between doses. The blame should go to the doctors if they are not monitoring their patients on a close basis.

Johnson et al. have successfully used buprenorphine in detoxifying patients from opiate dependence (48). Ling and Wesson also have successfully used buprenorphine to detoxify patients from methadone dependence (47).

In our view, the chronic pain of CRPS requires the use of strong non-addicting narcotics such as nubain, talacen, buprenorphine, stadol, and ultram. These medications are as strong if not stronger and safer then using addicting narcotics such as methadone, morphine, and ms contin.

Hunt and Bruera suggest that patients who start on MMT should be closely monitored for at least 1-2 weeks after starting their treatment (50). Patients should be continually monitored, even on a monthly basis to ensure no, side effects, and drug misuse or dependency issues.

According to Andrews et al. Methadone has been increasingly prescribed for chronic pain patients, yet the mortality rate has risen compared to other opioids (63). Since 1997 the use of Methadone has increased in the treatment of chronic pain across the United States (64).

The American Academy of Pain Medicine (AAPM) opposes the use of methadone as a preferred treatment option for chronic pain patients (65).

When Methadone is not used correctly, when not monitored, and when not prescribed properly, it is not a safe form of treatment and is proven to be linked to mortality.

We realize that there are a few of us rebelling against the recent surge of "liberal" pain prescriptions. However, we will keep warning the patients of the dangers of such drugs. The body usually signals the symptoms of complications of dangerous medication combinations. If something does not seem right to the patient, they should call their doctor or go to the emergency room right away.

We have just hit the tip of the iceberg with this growing “global epidemic” with reporting a few cases of CRPS patients dying from methadone toxicity (MT). We are sure that there are many others who have died from this unnecessary and unsafe form of treatment.

However, it's going to take a few years or decades to undo the damages that have been done with the use of such dangerous narcotics in the treatment of CRPS patients. It's also going to take a few decades for the medical community to rediscover, what has been discovered over the past decades, that the use of strong addicting narcotic such as methadone is going to cause more problems for CRPS patients rather than helping them.

The authors would like to dedicate this article to all CRPS patients who have lost their life to methadone.

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