Medication in the Management of Complex Regional Pain Syndrome (CRPS)

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Abstract: Complex regional pain syndrome (CRPS) is a syndrome defined as a state of constant burning and pain which is severe, incapacitating, and is aggravated by even a breeze or a simple touch to the involved area (allodynia).

In our review of 824 CRPS patients, the pain of CRPS is accompanied by swelling, inflammation, disturbance of the immune system function, movement disorder (flexion spasm, tremor, etc.) and emotional disturbance in the form of insomnia, depression, agitation, and irritability (1,2).

In CRPS, the chronic pain is not because of the abuse of drugs, the chronic pain is because of a delay in diagnosis and a delay in treatment. The other factor that causes the chronic pain in CRPS is inflammation which is part and parcel of CRPS. Anti-inflammatory medications such as mobic (meloxicam), voltaren (diclofenac) (gel or tablet), celebrex (celecoxib) are also helpful in the treatment of CRPS. With the help of the combination of the proper antidepressants (e.g., desyrel (trazodone), Zoloft (sertraline), paxil (paroxetine), and prozac (fluoxetine) as well as the use of strong non-addicting pain medications the patient will become pain free which is the key to the treatment of CRPS.

The symptoms of CRPS cannot be brought under control unless the pain is brought under control.

In this article, we will discuss which medications are helpful in the management of CRPS.

Keywords: *Complex Regional Pain Syndrome (CRPS), Antidepressants, Buprenorphine, Methadone, Trazodone.*

INTRODUCTION

The treatment for CRPS pain is quite different from the treatment of acute pain. In CRPS, the patient should definitely be treated with strong analgesics which are non-addicting. The best non-addicting analgesic is desyrel (trazodone) followed by other tricyclic antidepressants such as norpramin (desipramine). These medications have a naloxone reversible analgesic effect meaning that if they are taken along with narcan (naloxone) then they cannot control pain, otherwise they can. In this regard, they mimic the strongest narcotics and they are non-addicting. They raise the threshold of pain and they provide good analgesia along with more normal sleep pattern and along with by-product or side effect of being an antidepressant even though the patient usually in more than ¼ of the cases are not even depressed.

DIFFERENT TYPES OF PAIN

There are three different types of pain.

1. Acute pain such as a recent heart attack or car accident of a few weeks duration or a fracture of bone.

The treatment of choice for the acute pain is treatment with narcotics as well as correcting the damaged area by surgery or other methods which has originated the pain.

2. Cancer pain. In cancer pain the condition is called a "dynamic pain" which means there is a dynamic pathology ongoing damage in practically almost a continuous basis with both acute and chronic due to the infiltration of cancer cells and or due to multiple operations, or radiotherapy. In treatment of cancer pain, anything goes. The use of dolophine (methadone) is no problem and should be used. Other strong narcotic such as dilaudid(hydromorphone), MS Contin (morphine sulfate) or whatever treatment that relieves the patient's pain should be given. The patient has a short life expectancy and if sympathectomy relieves the pain, so be it (3). Even though sympathectomy is not indicated in CRPS patients, it can be done in cancer patients who have diabetes or severe occlusive disease of the blood vessels in the extremity. In such diabetic or severe occlusive disease patients or cancer patients, the life expectancy is usually less than 5 years and sympathectomy can provide a few years of relief. On the other hand, truly chronic pain and CRPS patients who are going to live several years or decades the sympathectomy is fraught with very high percentage of failure anywhere from a few weeks to 3 to 4 years after the sympathectomy is preformed (3).

3. The third type of pain is chronic pain and CRPS pain. In chronic pain, the original pathology has seized and has left scar and damage to the nerves. In some cases, the chronic pain has left the patient with no nerve damage but it is perpetuated because of the use of addicting (habituating and drug dependent) narcotics. On the other hand, in CRPS either the patient suffers from neuropathic pain (a pain that is due to neurovascular damage such as diabetic neuropathy) or sympathetically maintained pain (SMP) or further scar formation and involvement of the adjacent nerves due to scarring such as in the case of arachnoiditis which is the scar formation in the meninges of the spinal canal.

Patients suffering from CRPS should definitely be treated with strong analgesics which are not addicting.

As you can see treatment for chronic pain and CRPS pain is quite different from acute pain and should be treated accordingly.

ANTIDEPRESSANTS

Antidepressants are the analgesic of choice for treatment of persistent and long- standing pain for any cause. They are the treatment of choice not because the patient is depressed. A lot of patients suffering from chronic pain and CRPS are not depressed. The use of antidepressants is quite helpful because they provide analgesia (relief of pain), rest, and helps provide sleep, as well as counteracting depression.

This is a similar principle as is the case with aspirin. Aspirin is an analgesic, arthritis medicine, and prevents heart attack and stroke.

Whereas in acute pain, it is vital for the patient to take strong narcotics, in chronic pain such as CRPS it is vital for the patient to use antidepressants as an analgesic of choice.

However, antidepressant alone at the beginning of treatment is not enough. The patient has to be weaned off all addictive narcotics, and in the transition the patient needs to have strong pain medications which do not suppress the formation of endorphins.

Antidepressants are non-addicting. The use of antidepressants provides three beneficial therapeutic effects.

- Pain control
- Counteracting depression
- Helping the patient to be detoxified from addicting drugs

The use of trazodone in judicious careful doses provides an excellent REM sleep. The best time to take this medication is at bedtime and with the help of adjustment of the dosage and blood level of trazodone an accurate dosage can be figured for each patient. It is an excellent analgesic. However, it does have a tendency to mildly increase the appetite.

Antidepressants possess pure analgesic properties (4). An example is doxepin (zonalon) topical cream which is an excellent topical analgesic for neuropathic pain. The analgesic effect of tricyclics is reversed by naloxone (5). The analgesic property makes the therapeutic use of antidepressants essential for treatment of neuropathic pain (1,4).

Certain antidepressants such as tricyclics and trazodone, increase the synaptic serotonin and norepinephrine (nor ep) concentrations (6). This balanced phenomenon provides effective analgesia, natural sleep, and antidepressant effect (5). Trazodone provides analgesic effect in less than 24 hours in contrast with five to seven days for the same effective result with tricyclics (24). Trazodone does not cause weight gain when compared to amitriptyline(elavil) (1).

Of the tricyclics, amitriptyline has been the most widely used analgesic, but it has strong anticholinergic and sedative side effects, and my cause paranoid and manic symptoms (7,8).

More importantly, it has a tendency to cause weight gain. In our study of 824 CRPS patients, 612 had already been tried on amitriptyline (1). In the first year, these patients gained an average of over 7kg(15.4lbs), and in the following year, an additional 3.6kg(7.9lbs). Trial of desipramine or trazodone did not cause any significant weight gain. Weight gain in a CRPS patient who already has difficulty with ambulation is quite harmful (1).

The use of desipramine, is an excellent antidepressant and analgesic without the above-mentioned side effects of elavil. Even though antidepressants prevent pain, they do not replace the proper use of narcotic analgesics. The two are complimentary. Trazodone is as effective as desipramine or elavil in pain control.

It should be started in a small dose and gradually increased and adjusted upward or downward to achieve 8 hours of uninterrupted sleep, without the side effects of drowsiness the next day.

As is the case with any medication that influences the function of the brain, the patient should abstain from any alcohol intake while they are on antidepressant medication.

Antidepressants are important in improving the eventual recovery, immune system function, and reduction of mortality and morbidity in chronic pain and CRPS patients (9-11).

MORPHINE AGONISTS-ANTAGONISTS MEDICATIONS

STADOL (BUTORPHANOL TARTRATE)

One group of such strong pain medications that are not addicting are the so-called morphine agonists-antagonists' medications. One example is stadol (butorphanol tartrate) which is not even a controlled drug because it can be withdrawn at any time, "cold turkey" without causing any withdrawal or complications of addiction. It is true that psychologically the patients will develop an affinity to it and can abuse it from a psychological standpoint, but physiologically the Stadol does not interfere with the formation of endorphins and as such does not cause the three pillars of addiction (tolerance, withdrawal pain, and withdrawal physiological crisis of shaking, agitation, insomnia such as seen with withdrawal from addicting narcotics). Another example of such a group of medications is ultram (tramadol) which is also non-addicting and can be discontinued at any time without any problem.

Stadol is a synthetic opioid mixed agonist-antagonist analgesic. Of the three endorphin receptors in the brain (mu, theta, and kappa receptors), stadol has more affinity to mu and theta receptors. In therapeutic doses, the kappa receptor which is a larger sized receptor is not filled with the ligand stadol, and as a result, the endorphin fills the kappa receptor.

This explains the fact that in therapeutic doses, the Stadol does not stop the formation of the endorphin in the brain and in the spinal cord, and as a result, the patient does not develop withdrawal (rebound) phenomenon which is the main problem with opioid agonists such as morphine, etc.

However, if the dosage is increased above the therapeutic dose, then the stadol floods all the receptors, and the brain and the spinal cord stop forming natural endorphin. This explains the agonist as well as antagonist effect of Stadol in regard to pain relief. Opioid antagonists (stadol, nubain, or buprenorphine) in therapeutic dosage do not cause any serious problem. The problem comes when an opioid-agonists such as morphine, methadone, etc... is added to it, then the patient gets dry mouth, has drowsiness, and has nausea.

In addition, the use of stadol in high doses is as habit forming as morphine types of drugs.

This can cause stadol addiction and abuse (dependence). In this regard, the opioid antagonist acts similar to antebuse (disulfiram), they are supposed to make the patient very sick if the patient takes opioid agonists along with it. The above neuropharmacological principle explains the complexity of the agonist-antagonist analgesics.

BUPRENORPHINE (BUPRENEX)

Buprenorphine (buprenex), an opiate agonist-antagonist, is a strong analgesic without causing dysphoria, or dependence, (12-14). Sublingual buprenorphine has been used successfully for detoxification from cocaine, heroin and methadone dependence (12-14). Buprenorphine is a Class V narcotic in contrast to morphine, methadone or fentanyl, which are Class II.

Within the proper therapeutic window, buprenorphine (2-6mg/day) and Stadol (up to 14 mg/day), act as opioid antagonists by occupying only mu and delta receptors. In higher than therapeutic doses, they fill the kappa receptors as well, changing said drugs to pure opioid agonists and resulting in problems of rebound and tolerance (1,15,16).

Within 2-6mg per day, buprenorphine occupies mu and delta opioid receptors, but the kappa receptor is not occupied and is capable of receiving endorphins. When all three opioid receptors are occupied, endorphins cannot bind to them. Consequently, endorphin formation is ceased, leading to dependence and tolerance (1, 17).

Researchers from Harvard and others have found buprenorphine to act as an antidepressant leading to “a clinically striking improvement in both subjective and objective measures of depression” (1,18-20). This is in contrast to the common depressive effect of opioid agonists.

DOLOPHINE (METHADONE)

In our research, dolophine (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 patient's system for over 24-48 hours. 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 (21).

Methadone has been reported over the years to cause fatal overdoses (21-25). The primary toxic effect of methadone is respiratory depression and hypoxia; it can also cause pulmonary edema and/or aspiration pneumonia (21,26,27).

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" (21,28).

The use of methadone with increasing doses results in the patient not being motivated to be active and to get up and around. Secondarily the inactivity of the extremities wakes up the" sleeping nociceptors" and causes aggravation of pain. As the result, the patient needs to have more and more methadone. Eventually the dosage gets to the level of 10 to 20 mg 3 times a day up to even 50 mg 3 times a day. In such doses in the long-term basis, methadone causes intoxication of the brain such as seen among opiate addicts. This is in the form of prolonged bed rest, prolonged inactivity, drowsiness, and most importantly intoxication of the limbic system (the emotional centers of the brain).

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 than using addicting narcotics such as methadone, morphine, and ms contin (21).

Methadone treatment should not be applied to the treatment of CRPS patients.

ANTICONVULSANTS

Anticonvulsant treatment is helpful in CRPS for two types of symptoms (29,30):

- Spinal cord sensitization leading to myoclonic and akinetic attacks.
- In patients who suffer from ephaptic or neuroma type of nerve damage characterized by stabbing, electric shock, or jerking type of pain secondary to damage to the nerve fibres (31).

In such cases, anticonvulsants, especially tegretol **(**carbamazepine**)** (non-generic), depakene (valproic acid), gabapentin and klonopin (non-generic), are quite effective in treating CRPS (32-36).

The ephaptic, causalgic CRPS II is best managed with combination of an effective anticonvulsant, antidepressant, and analgesics.

If the patient needs to have an anticonvulsant for the sharp, stabbing, electric short type of pain (such as causalgia), addicting anticonvulsants such as barbiturates should be avoided.

The treatment of choice in these cases would be tegretol (carbamazepine) (non-generic) and/or neurontin (gabapentin).

Neurontin is the most over used medicine in the management of CRPS. The dosage of neurontin in children and the elderly is as low as 300-600 mg per day. In adults, it is 1800- 2600 mg per day, with a maximum of 3600 mg per day, anything above that dosage causes drowsiness, fatigue, inactivity, irritability, and depression. "The more is not the merrier."

MUSCLE RELAXANTS

Treatment with muscle relaxants is another important part of the treatment plan for CRPS patients who suffer from muscle spasms.

The constant component of CRPS is hypertonicity of the muscles in the form of vasoconstriction, flexion spasm, or movement disorder (3,37-46). It is imperative to treat the patient with muscle relaxants. The use of addicting muscle relaxants such as soma should be avoided. Soma is metabolized in the body and is transformed to meprobamate which is quite addicting and causes withdrawal with recurrence of muscle spasms. Flexeril which somehow has the reputation of being an antidepressant, is quite depressing and aggravates fatigue. It is quite effective in somatic type of muscle spasm, but not the sympathetic type.

The ideal muscle relaxant which works quite selectively on anterior lateral horn cells of the spinal cord is lioresal(baclofen) which helps relax the muscles as well as taking away the flexion spasms and enables the patient to get around (38).

This medicine should be started in small doses and gradually increased to a larger dose. The limiting factor is nausea. Once the patient develops nausea, then the dosage should be cut down by 5-10 mg and not increased any further.

Another effective muscle relaxant is norflex (orphenadrine). If the patient has muscle spasms along with jerky movement and dystonic motion of the extremity, the use of anticonvulsants such as klonopin, neurontin, tegretol, depakene and trileptal (oxcarbazepine) may be beneficial.

ANTI-INFLAMMATORY MEDICATIONS

In CRPS, the inflammation of the disease is usually mistaken for carpal tunnel, tarsal tunnel, TOS, arthritis, and rotator cuff syndrome. The unnecessary surgical treatments severely aggravate the neuroinflammation.

The use of nonsteroidal anti-inflammatory medications such as mobic (meloxicam), voltaren (diclofenac) (gel or tablet), celebrex (celecoxib), and anaprox (naproxen) are quite helpful in treating the neuro-inflammation of CRPS.

In our clinic, we have also noted the beneficial effect of using i.v. mannitol in the treatment of neuroinflammation. This is especially true in patients suffering from CRPS, post-herpetic neuralgia, and other forms of neuropathic pain.

Mannitol has been used for many decades as an effective intracellular type of diuretic.

The use of mannitol is very well tolerated in most patients. The only contraindications are in patients who have practically total renal failure and in patients who already have a dead space of intra-cerebral hemorrhage or necrotic brain tumor, which can cause entrapment of the mannitol in the dead space.

In our clinic and as well as Doctor Veldman's group in the Netherlands have applied i.v. mannitol to counteract neurogenic edema (1,47). Such neurogenic edema is especially more prominent in patients who have undergone such surgeries as sympathectomy, infusion pump, and spinal cord stimulators(SCS). At times the neuroinflammation is severe enough to cause a skin rash and neurodermatitis as well.

The usual dose of mannitol in the treatment of CRPS is 100gm in 500cc D5W. Mannitol has a tendency to crystallize, the i.v. should be applied for 1-1 ½ hours. If the i.v. drip is prolonged up to 4-6 hours, there is the risk of crystallization of the mannitol. Certainly, a filter should help prevent any such risk as well.

As long as the patient has a normal renal clearance (no protein in the urine), the use of i.v. mannitol treatment is quite safe and helpful in reducing the neuroinflammation of CRPS.

CONCLUSION

One must realize that treating patients suffering from CRPS is a very complex task. Many of these patients have suffered for many years with the chronic unrelenting pain of CRPS. Most patients have been mistreated with unnecessary procedures and strong additive pain medications that have caused more pain and harm to the patient.

Over the years, we have seen all forms of treatment applied to CRPS patients, some of which are quite helpful and some which are nonsensical. Some patients are treated with a combination of strong addictive narcotics in unlimited dosage. Some are given duragesic patch, MS Contin, methadone and other forms of strong addicting narcotics.

In such patients, the disease progresses rapidly from stages I to II all the way to stage IV (disturbance of immune system, suicidal attempts or successful suicide, heart attack, stroke, and severe hypertension). The problem becomes more complicated due the simultaneous use of strong addicting tranquilizers such as valium, xanax, ativan, halcion, and a slew of other addicting benzodiazepams (BZS). Such addicting tranquilizers should also be discontinued with the help of tapering the patient off from the addicting tranquilizer, simultaneously replacing it with non- addicting benzodiazepams (e.g., klonopin) until the patient is complete detoxified after several weeks or months.

One must also consider adding an antidepressant to the patient's treatment plan in a safe enough dosage (guided by blood level of antidepressant) to help control the pain and symptoms of CRPS.

With the help of the combination of proper antidepressants (e.g., desipramine or trazodone) as well as the use of strong non-addicting pain medications such as buprenorphine, stadol, and ultram which are helpful and a safer alternative in the treatment of CRPS. This type of a treatment plan could be very beneficial in helping the patients pain and symptoms of CRPS.

However, it is going to take a lot of education to help the medical community, CRPS patients and their caregivers to understand that there are other safer non-addictive pain medication alternatives available when it comes to treating this complex syndrome of CRPS.

References:

1. Hooshmand H, Hashmi H. Complex regional pain syndrome (CRPS, RSDS) diagnosis and therapy. A review of 824 patients. *Pain Digest* 1999; 9:1-24. http://www.rsdrx.com/CRPS_824_Patients_Article.pdf

2. Hooshmand H, Phillips EM. Psychological Aspects of Reflex Sympathetic Dystrophy (RSD) Complex Regional Pain Syndrome (CRPS). http://www.rsdinfo.com/Psychological_Aspects_of_RSD.pdf

3. Hooshmand H. Chronic Pain: Reflex Sympathetic Dystrophy: Prevention and Management. CRC Press, Boca Raton FL. 1993. http://www.rsdrx.com/Dr._Hooshmand-s_RSD_Text_Book.pdf

4. McQuay HJ, Tramer M, Nye BA, et al. A systematic review of antidepressants in neuropathic pain. *Pain* 1996; 68:217-227. https://www.ncbi.nlm.nih.gov/pubmed/9121808

5. Ardid D, Guilbaud G. Antinociceptive effects of acute and 'chronic' injections of tricyclic antidepressant drugs in a new model of mononeuropathy in rats. *Pain* 1992; 49: 279-287. http://www.sciencedirect.com/science/article/pii/0304395992901522

6.Goodkin K, Gullion C, Agras WS. A randomized, double-blind, placebo-controlled trial of trazodone hydrochloride in chronic low back pain syndrome. *J Clin Psychopharmacol* 1990; 10:269-278. http://www.medscape.com/medline/abstract/2149565

7. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. *Arch Intern Med* 1997; 157:1531-1536. http://jamanetwork.com/journals/jamainternalmedicine/article-abstract/623574

8. Patten SB, Love EJ. Drug-induced depression. Incidence, avoidance, and management. *Drug Safety* 1994; 10:203-219. https://rd.springer.com/article/10.2165/00002018-199410030-00003?no-access=true

9. Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. Circulation 1995; 91: 999-1005 https://doi.org/10.1161/01.CIR.91.4.999

10. Fedoroff JP, Lipsey JR, Starkstein SE, et al. Phenomenological comparisons of major depression following stroke, myocardial infarction or spinal cord lesions. *J Affect Disord* 1991; 22:83-89 https://www.ncbi.nlm.nih.gov/pubmed/1880312

11.Leserman J, Petitto JM, Perkins DO, et al. Severe stress, depressive symptoms, and changes in lymphocyte subsets in human immunodeficiency virus-infected men: a 2-year follow-up study. *Arch Gen Psychiatry* 1997; 54: 279-85 http://jamanetwork.com/journals/jamapsychiatry/article-abstract/497781

12. Ling E, Wesson DR, Charuvastra C, et al. A controlled trial comparing buprenorphine and methadone, maintenance in opioid dependence. *Arch Gen Psychiatry* 1996; 53:401-407. http://jamanetwork.com/journals/jamapsychiatry/article-abstract/497574

13. Johnson RE, Jaffe JH, Fudala PJ. A controlled trial of buprenorphine treatment for opioid dependence. *JAMA* 1992; 267:2750-2755. http://jamanetwork.com/journals/jama/article-abstract/397410

14. Schottenfeld R, Pakes JR, Oliveto A, et al. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Arch of Gen Psychiatry* 1997; 54:713-720. http://jamanetwork.com/journals/jamapsychiatry/article-abstract/497875

15. Eissenberg T, Greenwald MK, Johnson RE, et al. Buprenorphine's physical dependence potential: antagonist-precipitated withdrawal in humans. *J Pharmocol Exp Ther* 1996; 276:449-459.https://www.researchgate.net/publication/14568870_Buprenorphine%27s_physical_dependence_potential_Antagonist-precipitated_withdrawal_in_humans

16. Riley AL, Pournaghash S. The effects of chronic morphine on the generalization of buprenorphine stimulus control: an assessment of kappa antagonist activity. *Pharmacol Biochem Behav* 1995; 52: 779-787. http://www.sciencedirect.com/science/article/pii/0091305795001805

17. Faught E, Wilder BJ, Ramsay RE, et al. Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages. *Neurology* 1996; 46: 1684-1690. https://www.researchgate.net/publication/14550134_Topiramate_placebo-controlled_dose-ranging_trial_in_refractory_partial_epilepsy_using_200-_400-_and_600-mg_daily_dosages_Topiramate_YD_Study_Group

18. Bodkin JA, Zornberg GL, Lukas SE, et al. Buprenorphine treatment of refractory depression. *J Clin Pyschopharmacol* 1995; 15: 49-57. https://www.ncbi.nlm.nih.gov/pubmed/7714228?dopt=Abstract

19. Emrich HM, Vogt P, Herz A. Possible antidepressive effects of opioids: action of buprenorphine. *Ann NY Acad Sci* 1982; 398: 108-112. https://www.ncbi.nlm.nih.gov/pubmed/6760767

20. Gold MS, Pottash ALC, Sweeney DR et al. Rapid opiate detoxification: clinical evidence of antidepressant and antipanic effects of opiates. *Am J Psychiatry* 1979; 136: 982-983. https://www.ncbi.nlm.nih.gov/pubmed/453367

21. Phillips EM, Hooshmand H (Retired). Methadone Related Deaths (MRD) Among Complex Regional Pain Syndrome (CRPS) Patients. http://www.rsdinfo.com/Methadone_Related_Deaths_-MRD-_Among_Complex_Regional_Pain_Syndrome_-CRPS-_Patients.pdf

22. Drummer OH, Opeskin K, Syrjanen M, et al. Methadone toxicity causing death in ten subjects starting on a methadone maintenance program. *Am J Forensic Med Pathol* 1992; 13(4):346–350. https://www.ncbi.nlm.nih.gov/pubmed/1288269

23. Baden MM. Methadone related deaths in New York City. *Int J Addict* 1970; 5: 489–498. https://www.ncbi.nlm.nih.gov/pubmed/5524383

24. Gardner R. Methadone misuse and death by overdosage. *Br J Addict* 1970; 65(2):113–118. http://onlinelibrary.wiley.com/doi/10.1111/j.1360-0443.1970.tb01141.x/full 16

25. Clark JC, Milroy CM, Forrest ARW. Deaths from methadone use. *J Clin For Med* 1995; 2:143-144. http://onlinelibrary.wiley.com/doi/10.1111/j.1360-0443.1970.tb01141.x/full

26. Harding-Pink D. Methadone: one person's maintenance dose is another's poison. *Lancet* 1993; 341(8846):665–666. https://www.ncbi.nlm.nih.gov/pubmed/8095576

27. White JM, Irvine RJ. Mechanisms of fatal opioid overdose. *Addiction* 1999; 94: 961–972. https://www.ncbi.nlm.nih.gov/pubmed/10707430

28. Approved new drugs requiring continuation of long-term studies, records, and reports; listing of methadone with special requirements for use. Federal Register December 15, 1972; 37(242):26790. https://cdn.loc.gov/service/ll/fedreg/fr037/fr037242/fr037242.pdf

29. Rull JA, Quibrera R, Gonzalez-Millan H, et al. Symptomatic treatment of peripheral diabetic neuropathy with carbamazepine (Tegretol): double blind crossover trial. *Diabetologia* 1969; 5:215-218 https://link.springer.com/article/10.1007/BF01212087

30. McQuay HJ. Pharmacological treatment of neuralgic and neuropathic pain. *Cancer Surv* 1988; 7:141-159 https://www.ncbi.nlm.nih.gov/pubmed/?term=McQuay+HJ.+Pharmacological+treatment+of+neuralgic+and+neuropathic+pain.+Cancer+Surv+1988%3B+7%3A141-159

31. Thompson JE. The diagnosis and management of post -traumatic pain syndromes (causalgia) *Aust NZ J Surg* 1979; 49:299-304 https://www.ncbi.nlm.nih.gov/pubmed/289369

32. McQuay H, Carroll D, Jada AR, et al. Anticonvulsant drugs for management of pain: a systemic review. *BMJ* 1995; 311:1047-1052 http://www.bmj.com/content/311/7012/1047.long

33. Mellick GA, Mellick LB. Reflex sympathetic dystrophy treated with gabapentin. *Arch Phys Med Rehabil* 1997; 78:98-105 http://www.archives-pmr.org/article/S0003-9993(97)90020-4/pdf

34. Swerdlow M, Cundill JG. Anticonvulsant drugs used in the treatment of lancinating pain. A comparison. *Anaesthesia* 1981; 36:1129-1132 https://www.ncbi.nlm.nih.gov/pubmed/6798892

35. Reddy S, Patt RB. The benzodiazepines as adjuvant analgesics. *J Pain Symptom Manage* 1994; 9:510-514 http://www.sciencedirect.com/science/article/pii/0885392494901120

36. Hooshmand H. Intractable seizures. Treatment with a new benzodiazepine anticonvulsant. *Arch Neurol* 1972; 27:205-208 http://jamanetwork.com/journals/jamaneurology/article-abstract/571613

37. Hooshmand H, Phillips EM. The management of complex regional pain syndrome(CRPS) http://www.rsdrx.com/THE_MANAGEMENT_OF_CRPS.pdf

38. Gowers WR. A manual of diseases of the nervous system. Churchill. London. 1888.

39. Jankovic J, Van Der Linden C. Dystonia and tremor induced by peripheral trauma: predisposing factors. *J Neurol Neurosurg Psychiatry* 1988; 51:1512-1519. http://jnnp.bmj.com/content/jnnp/51/12/1512.full.pdf

40. Cardoso FE, Jankovic J. Hereditary motor-sensory neuropathy and movement disorders. *Muscle Nerve* 1993; 16: 904-910. http://onlinelibrary.wiley.com/doi/10.1002/mus.880160904/abstract

41. Mitchell, G.A.G. Anatomy of the autonomic nervous system. E & S Livingstone Ltd, Edinburgh 1953. https://archive.org/details/in.ernet.dli.2015.121058

42. Schott GD. Induction of involuntary movements by peripheral trauma: an analogy with causalgia. *Lancet* 1986; 2: 712-716. https://www.ncbi.nlm.nih.gov/pubmed/2876186

43.Scherokman B, Husain F, Cuetter A, et al. Peripheral dystonia. *Arch Neurol* 1986; 43:830-832. http://jamanetwork.com/journals/jamaneurology/article-abstract/585624

44. Brin MF, Fahn S, Bressman SB, Burke RE. Dystonia precipitated by trauma. *Neurology* 1986; 36(4):119 supplement I. https://insights.ovid.com/neurology/neur/1986/04/001/dystonia-precipitated-peripheral-trauma/148/00006114

45. Fletcher NA, Harding AE, Marsden CD. The relationship between trauma and idiopathic torsion dystonia. *J Neurol Neurosurg Psychiatry* 1991; 54: 713-717. http://europepmc.org/articles/PMC1014477

46. van der Laan L, Veldman PH, Goris RJ. Severe complications of reflex sympathetic dystrophy: infection, ulcers, chronic edema, dystonia, and myoclonus. *Arch Phys Med Rehabil* 1998; 79: 424-429. http://www.sciencedirect.com/science/article/pii/S0003999398901447

47. Veldman PH, Goris RJ: Sequelae of reflex sympathetic dystrophy. Clinic Aspects of Reflex Sympathetic Dystrophy. Thesis: 1995; Chapter 10, Pgs. 119-129.