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Educational case report

Chronic non-cancer pain and the long-term efficacy and safety of opioids: Some blind men and an elephant?☆

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ABSTRACT

Background: The use of opioids for chronic non-cancer pain (CNCP) remains very controversial. There are a number of randomized controlled trials (RCTs) showing efficacy and safety in the short-term, but long-term data are limited.
Methods: This article contains 10 case reports (followed to 2011) that were selected from a survey of 84 patients with intractable CNCP treated with opioids and followed every 3 months now for a median of 10 years. The previous published survey of this group reported outcomes of pain severity, adverse effects, pain relief, satisfaction, mood, problematic opioid use, tolerance, physical dependency, functional status, health-related quality of life (HRQL), immune status and sexual function. The outcome measures for that study included a numerical rating scale (NRS) for pain, Hospital Anxiety and Depression Scale (HADS), the Brief Pain Inventory Interference Scale (BPI-I), the Pain Disability Index (PDI), and for Health Related Quality of Life (HRQL) the Short Form Health Survey 12 version 2 (SF12v2). These selected patient reports were chosen to illustrate some important aspects of the diagnostic categories of CNCP, the opioids and doses used, particular issues (concurrent addiction history, bipolar disorder, and combination therapy), disease-specific and other outcomes (pain severity and relief, adverse effects, mood, function) and duration of follow-up with complex pain problems.
Results: Opioids were found to be safe and effective in the long-term for these particular patients, as well as in the larger group from which they originate. Most patients in the total sample reported 50% or greater relief and a moderate improvement in disability. Scores for functional status and HRQL were not severely affected (PDI and BPI-I ratings moderate or less and SF12v2 slightly below normative values for age). Problematic use, tolerance, and serious adverse effects including constipation were not major issues.
Conclusion: These 10 reports of patients with intractable CNCP treated with opioids with some success over many years put a face on some of the participants in the larger survey of 84 suggesting that this approach is effective and safe for some patients over many years.
Implications: These data may not be generalizable to a larger population of patients with CNCP because of the probable selection of patients who benefit and who do not have intolerable adverse effects.
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1. Introduction

"We see a pattern of increasing use (of opioids) despite lack of evidence for effectiveness. When it is not working, we have been taught to increase the dose until it is, although experience has taught that if it is not working, it is not going to work. Worse still, high doses are associated with toxicity and the refractoriness that may make it impossible to treat pain effectively. We are providing a treatment that for many patients is not improving their pain but is compromising their lives and futures" [1].

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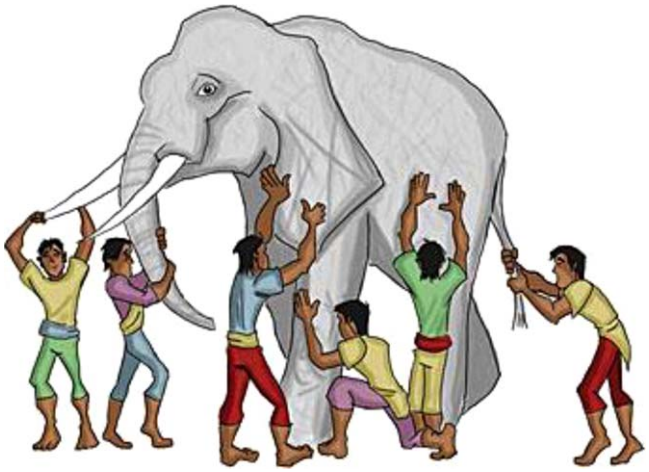

The third approached the animal,
And happening to take
The squirming trunk within his hands,
Thus boldly up and spake:
"I see" quoth he, "the elephant is very like a snake!"
Folk tale: The blind men and the elephant

We have come to a point where we have to decide whether the quotation that initiates this section is true or is an extreme, rather Draconian, view. The current controversy about the long term efficacy and safety of opioids in chronic non-cancer pain (CNCP) may be likened to the story of the visually challenged men and the elephant. In this tale each individual has a different piece of the beast in his hands and draws a different conclusion about its nature. In this instance these individuals could include: those involved in pain treatment, addiction medicine specialists, clinical trialists, epidemiologists, the police, coroners, pharmacists, the television and print media, family physicians and the public (especially those who have lost loved ones to the ravages of addiction). An extrapolation of this tale may be to ponder that, even when the whole animal is correctly identified, the question remains as to whether it is a trainable Indian elephant perhaps prone to an occasional rampage or the completely unmanageable African version.

Chronic pain is common in populations in North America and European countries such as Denmark. A stable figure of 20% of the Danish population suffer from mostly CNCP [2–4] and a recent report, consistent with this, from the American state of Kansas reported a figure of 26% [5]. These numbers are similar to a WHO figure of 20% of the world's population having some degree of chronic pain [6]. Denmark has for years had a high use of opioids mostly for CNCP [7,8]. A similar situation is present in North America where there has also been an increase in the use of opioids for CNCP. As well, a reported increase in the abuse of and deaths associated with opioids has been documented [9,10]. The latter has been related to the daily dose used [11].

Despite a number of randomized controlled trials (RCTs) of opioids in CNCP showing efficacy and safety in the short term [12–20], the long-term use of opioids for these conditions remains controversial in view of concerns about long-term efficacy and safety. Efficacy concerns include pain relief, tolerance, improvement in function and health-related quality of life (HRQL). Safety concerns include the risk of problematic use and diversion, increased pain sensitivity such as hyperalgesia with high doses, potential effects on the immune and endocrine systems, cognitive/affective changes and mortality from overdosage [21–28].

Minimal data are available regarding the long-term effects in CNCP patients treated with opioids. It is difficult to conduct an RCT over long periods of time and data in this regard are both observational [29–34] and epidemiological [4,5,35–37]. A recent Canadian publication [9] reported increased deaths associated with multiple drugs including opioids in a population-based database of people on social assistance (thus likely in poor physical and/or mental health and over 65 years of age). How many of these deaths occurred in addicts, persons experimenting or pain patients is unknown. As well, television and print journalists' articles and newspaper reports of coroner's inquests into addict deaths have created a frigid atmosphere for opioid prescribing especially by family physicians; however, pain clinics and specialists cannot handle the volume of CNCP patients without long wait times. This situation is somewhat reminiscent of the 19th century when patent medicines containing opioids were unconstrained, readily available and prescribed for a variety of disorders, even as a tonic, resulting in widespread psychological dependency and extreme opioid phobia which endured into the mid 20th century. This was not helped by biased data from the addict population indicating that many addicts stated that they had become addicted by opioid prescriptions for medical problems. Unfortunately, ponderous but necessary guidelines are often relegated to gathering dust on the "to be read" shelf and may not help to alter practice. An important caution in prescribing higher opioid doses has been voiced [1] especially if the prescriber is not adequately educated about analgesics. However recent suggestions have been made that certain opioids be banned and dose ceilings for others be legislated. These recommendations have the potential to threaten the timely and adequate treatment of those with severe, disabling CNCP some of whom may only respond to opioids and sometimes require high doses. It is timely and of great importance that we document and put a face on the patients who benefit substantially particularly in disease-specific outcomes (ability to wear clothing in postherpetic neuralgia or to use a prosthesis in phantom pain) and only from these drugs for long periods of time safely. The purpose of this article is to describe details of a case series of 10 patients with intractable CNCP on long-term opioids followed for many years up to 2011, selected from a 2007 survey [34] and seen regularly now for a median of 10 (range 4–27) years.

2. Methods

This case series of 10 patients was selected and updated to 2011 from a group of 84 patients with intractable, daily, severe CNCP treated with opioids for at least one year, living in the community followed regularly every 3 months and surveyed in 2007 in detail between September 1 and December 31, 2007 [34]. Intractable means that they were refractory to non-opioid medications having had adequate trials of non-prescription analgesics, at least two analgesic antidepressants and anticonvulsants, topical agents (lidocaine, capsaicin) and offered surgical procedures when appropriate. Patients with the CNCP of fibromyalgia and most with chronic headache were excluded. Informed consent was obtained from all patients. The photographs have been included with permission from each patient. Reported here in more detail are the diagnostic categories, the opioids and doses used, level of function, disease-specific outcomes (ability to wear clothes, use a prosthesis), mood, presence of tolerance and duration of follow-up. A standard conversion table was used for calculating morphine equivalents [50].

3. Case reports

Case 1: JB (Fig. 1) is a 43-year-old man who has been followed for 8 years with phantom limb pain treated with a stable dose of long-acting oxycodone (540 morphine equivalents/day) for 4 years. Twenty-four years ago he had a right above knee amputation after

Fig. 1. JB: this patient has been able to enjoy a good quality of life by suppressing phantom limb pain with opioids for 8 years.

a motor cycle accident. He had suffered severe, steady, burning pain in the phantom toes and ball of the right foot averaging 8/10 day and night previously for 16 years. There was no response to amitriptyline, nortriptyline or gabapentin titrated to intolerable adverse effects. There was no stump pain and the physical examination was normal apart from the amputation. His pain now averages 2–3/10 with stable dosing of his opioids over 4 years. He has no significant adverse effects including constipation for which he takes nothing. He can wear his prosthesis without difficulty. He runs a company employing 10 and can drive, fish and play golf three times a week (Fig. 1) His mood is good. Qualitatively he states that "I have my life back" and "It is the difference between night and day".

Comment: This man's case represents an exceptionally good response of phantom limb pain to a high dose of long-acting oxycodone with a high level of functioning, no significant adverse effects and improved disease-specific outcome (ability to wear his prosthesis, golf and fish) for 8 years unchanged for four years with no evidence of harm.

Case 2: DF is a 63-year-old man who was seen 15 years ago with a 9 year history of back and left first sacral nerve root pain and left knee pain. This problem originated with a work injury consisting of a fall. He had had three left knee replacements and an MRI showed a large disc herniation at L 5/S1 resulting in two back surgeries. The left knee and sciatic pains were a steady pain rated at 10/10 for half the day with activity and 6/10 for the rest in recumbency (day and night) but worse with activity. He used oxycodone (morphine equivalent of 45 mg/day)/day which reduced the pain to 2/10 for 2–3 h. The pain was localized to the low back, posterior thigh and calf and to the left knee. Examination revealed a fused left knee, sciatica at 20° of straight leg raising and an absent left ankle reflex. Over the ensuing 4 years he had 4 more left knee replacements and 6 other surgeries for osteomyelitis of the knee with trial and error opioids and dosages as the disease progressed and his pain increased but always with pain reduction as opioid doses increased and no evidence of hyperalgesia. Five years ago his pain stabilized at 2–3/10 with activity which he states is an 80% improvement. The opioid regimen has remained the same for 5 years to the present on transdermal fentanyl, long-acting hydromorphone, long-acting oxycodone, short-acting hydromorphone and short-acting oxycodone (1650 mgm morphine equivalents/day). The leg

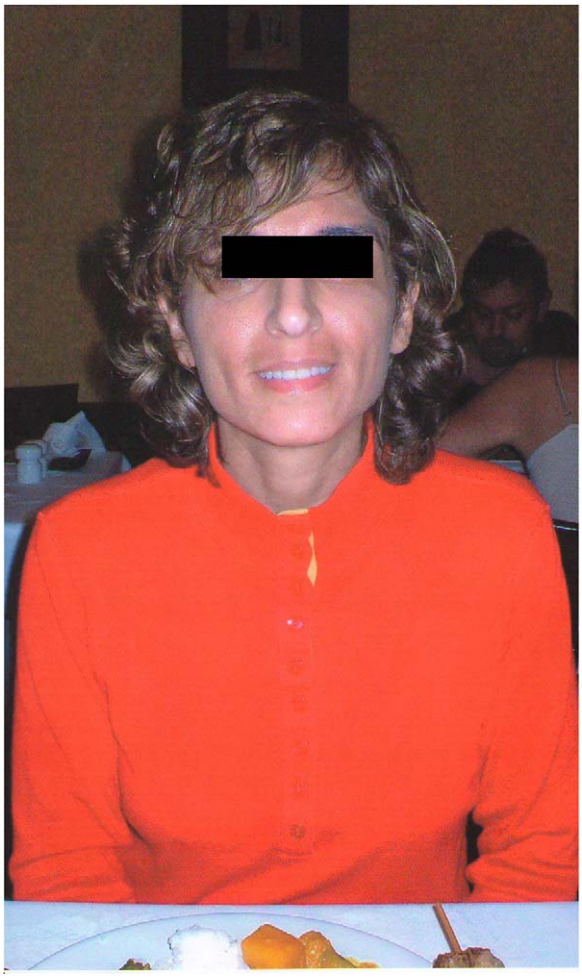

Fig. 2. NS: this patient is now able to maintain her weight by the relief of visceral pain provoked by eating by taking morphine before each of six daily meals. She has been on this regimen for 11 years.

was amputated in 2009 with a revision for infection and he is now well with a prosthesis and on the same opioids and doses with pain 1–2/10. He now has the pain in the phantom foot, and has no stump pain and continues with mild (2–3/10) burning and shock-like pain in the back and posterior leg. His mood is good and he has no significant adverse effects including constipation which he manages with docusate. Dose reduction results in pain levels of 10/10. He has been able, with opioids, to help with gardening, ride a lawn tractor and chip a golf ball.

Comment: This man required very high doses of a combination of opioids, stable for 5 years, arrived at by sequential trial and error and titration of one before another was added for optimal pain control without evident harm and good function for 15 years despite very severe pain due to recurrent, progressive and life-threatening disease with three (sciatica, osteomyelitis, orthopedic) and then (with phantom pain after amputation) four major causes for his intractable pain.

Case 3: NS (Fig. 2) 41-year-old female seen 15 years ago with a 4 year history of abdominal pain after eating. She had a history of a total gastrectomy and gastro-jejunal anastomosis due to bleeding ulcers. She was, at first assessment, bedridden and weighed 80 lb. She attempted 6 small meals a day but suffered severe epigastric pain and nausea. She noticed that previously treatment with oral meperidine and pentazocine helped her eat more but she was unable to obtain these long-term. She was titrated up to 40 mg of oral morphine 45 min before each of 6 meals and was able to eat more

without discomfort or nausea. The same dose has been used for 15 years. She regained her former normal weight and returned to all activities including a full-time job. Her mood is good, she has no side effects including constipation and said she is very satisfied with her treatment. She said "I have my life back' and "more than that I have my livelihood back" and also "It is like night and day".

Comment: This woman has had a very good response for visceral pain for 15 years with stable doses of 240 mg/day of short-acting morphine in divided doses before meals without apparent harm and good function in the disease-specific outcome of her ability to eat. She continues to be seen every 3 months in the absence of a family practitioner's support. Putatively the morphine may be acting locally on opioid receptors in the bowel.

Case 4: HS is a 56-year-old man who was seen 6 years ago and had very severe back and neuropathic leg pain bilaterally from surgically visualized scar tissue for 8 years and had had three previous surgeries. He was bedridden or chair-bound, refractory to all medications including gabapentinoids and tricyclic antidepressants. He had been treated with several opioids and had a very slight response to sustained-release oxycodone at a dose of 1000 mg morphine equivalents per day. At this point, he was still rating his pain as 8–10/10 and refused any further procedures. Due to the occasional rating of his pain at 8/10 (from 10/10) on oxycodone and, in the face of his severe disability, after a thorough discussion of risks and benefits and re-assessment of risk factors, his dose of long-acting oxycodone was increased to a total of 2000 mg of morphine equivalents per day. His pain is now reduced from 9–10/10 to 6/10. He is able to get out of bed, be up and about the apartment, get meals, do light housework, and go for short walks. He is able to fly with his son several hundred miles and travel while there in a car. He has now been followed on opioids for 5.5 years and has been on the same dose for 3 years, his mood is good and he has no significant side effects and tolerable constipation.

Comments: In the face of almost complete intractability to all measures, severe disability and a high dose of opioid and in the presence of no side effects of note the dose of opioid was increased further. This regime slowly reduced pain to a moderate level enabling him to get out of bed and resume activities of daily living, fly and sit in a car for 2–3 h. There was no evidence of hyperalgesia as the dose was slowly increased. He has no drowsiness and for 3 years has driven himself 20 miles to his appointment and back every 3 months.

Case 5: NH is a 36-year-old female first seen 6 years ago with a 20 year history of rheumatoid disease with severe (10/10) pain in the joints of her hips, knees, ankles, shoulders, elbows, wrists and fingers despite some relief with a TNF inhibitor (7–8/10) but no effect of gold injections, NSAIDS and corticosteroids (methylprednisolone 1000 mgm IV/day × 5 days). Generalized joint tenderness and swelling were present. Her weight was 160 lb. Titration with long-acting oxycodone every 8 h (1400 morphine equivalents/day) resulted in pain severity with activity of 3/10. This has been unchanged for 5 years. There was no sign of hyperalgesia as with dose titration pain gradually decreased. She has no significant side effects, including constipation managed with stool softeners, her mood is good and she is able to attend law school fulltime.

Comment: In this instance the treatment of chronic, severe, intractable arthritic pain has resulted in good pain relief over a long period of time with no significant side effects and a good quality of life. Both the TNF inhibitor and opioid seem to have an additive effect and both are necessary for optimal relief.

Case 6: WG (Fig. 3) is a 52-year-old man seen 14 years ago with a 5 year history of severe (10/10) steady, burning and shock-like pain from anesthesia dolorosa of the right side of the face. This occurred after a radiofrequency lesion for chronic cluster headache. There was no recurrence of the cluster headache. He had failed to find relief with gabapentinoids or tricyclic antidepressants and was unable to work. On examination he had sensory loss over the right trigeminal nerve territory to pin, cold and touch with no allodynia. Gradual titration with morphine established a dose of 300 mg/every 8 h of long-acting morphine which has been unchanged for 10 years with no significant side effects. Constipation is tolerable with stool softeners and senna tea. After opioid initiation he ran his own restaurant franchise until retirement, then supervised the building of his own retirement home and now buys, develops and sells real estate. He drives 200 miles and back to his appointment every 3 months with no drowsiness. He now has no apparent impairment of his life, his mood is good and he is quite satisfied with the relief and tolerability of the morphine.

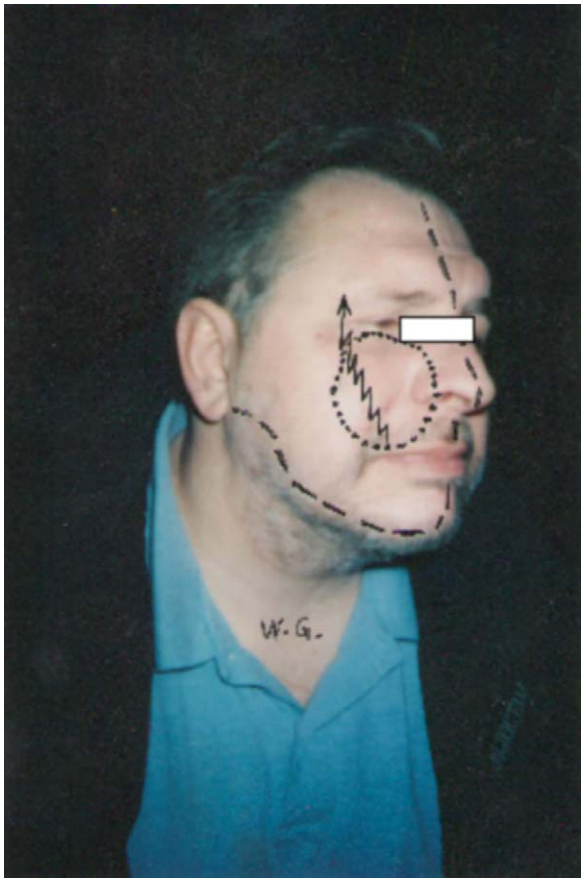

Fig. 3. WG: this patient developed trigeminal anesthesia dolorosa after a radiofrequency lesion for right sided chronic cluster headache. Area of sensory loss – all of the right trigeminal nerve area (interrupted line). Area of steady pain in maxillary ramus of the right trigeminal nerve (dotted line). Shock-like pain from upper lip area (jagged line). He has been on opioids for 10 years.

Comment: This is an example of a rare form of neuropathic pain (NP), anesthesia dolorosa. This is often very difficult to relieve as it had been for 5 years for WG. He has had excellent long-term relief for 10 years by high dose morphine with tolerable side effects and no apparent harm.

Case 7: RL (Fig. 4) is a 54-year-old female first seen 18 years ago with severe (10/10) steady, burning NP in the left arm due to brachial plexus avulsion. She also had severe left knee pain, fusion of the left knee, moderate (6/10) pain in the low back, left knee and neck and multiple fractures of facial bones, brain injury and coma for a week occurring when her car was hit by a train 2 years previously. She had a history of bipolar disorder, alcoholism and oxycodone addiction 8 years previously and was considered recovered by her addiction medicine specialist. She declared herself desperate and suicidal. She had received antidepressants, anticonvulsants, codeine and pentazocine without good relief. There was

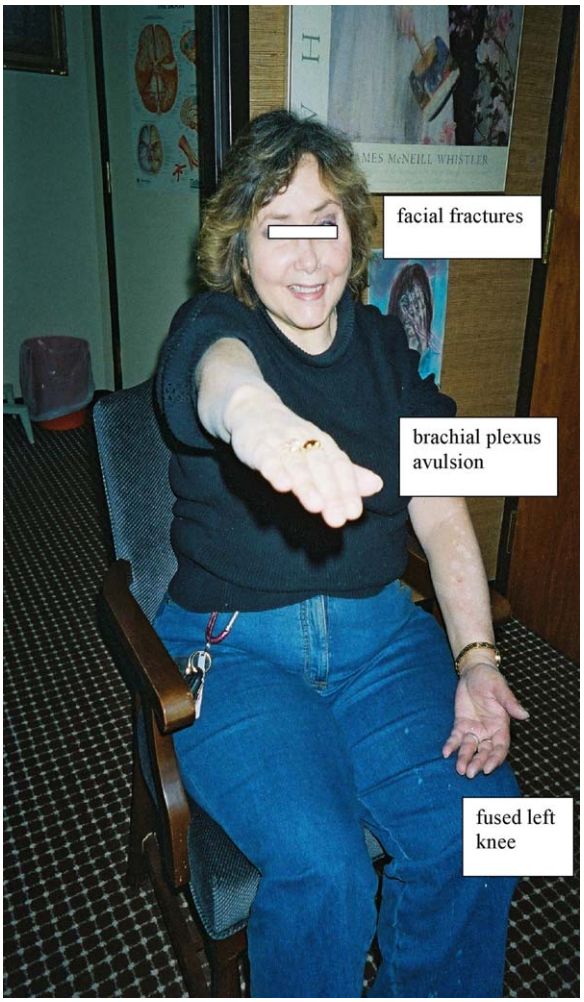

Fig. 4. RL: this woman has a complex pain condition after a major accident in which her car was hit by a train. She had a history of alcohol and drug abuse, bipolar disorder and was seriously suicidal. In spite of these red flags she was successfully maintained on oxycodone and a fentanyl patch for 18 years.

understandable reluctance on the part of her physicians to treat her with opioids. Examination revealed paralysis and atrophy of the left arm, exquisite allodynia in C5–6, some function of C5, 6 innervated muscles, a crush injury of the left face with cosmetic deformity from scarring and boney injury, loss of vision in the left eye and a fused left knee. She was bedridden and feeling hopeless. A number of red flags (bipolar disorder, addiction history, family history of addiction and mild cognitive impairment from her head injury) were present. Because she appeared to be a major suicide risk a decision was made to institute opioid treatment under very close supervision and with concurrent psychiatric care. She was tried on a variety of opioids and ultimately her pain came under control (2–4/10) on transdermal fentanyl and oxycodone (1500 mg morphine equivalents daily), as well as paroxetine and bupropion. She has been on the same dose for 6 years. She manages constipation with milk of magnesia. She lives alone, her mood is stable, she is now active in activities of daily living, socializes and exercises in a pool regularly. She drives 30 miles to her appointment every 3 months. Her facial deformity has been cosmetically repaired and nerve grafting has given her some useful function of her left arm. She has had one episode 10 years ago of abuse of hydromorphone during a manic episode subsequently controlled with mood stabilizing agents. RL states that "my pain is controlled and without the patches I am suicidally depressed because of pain and would not be alive today."

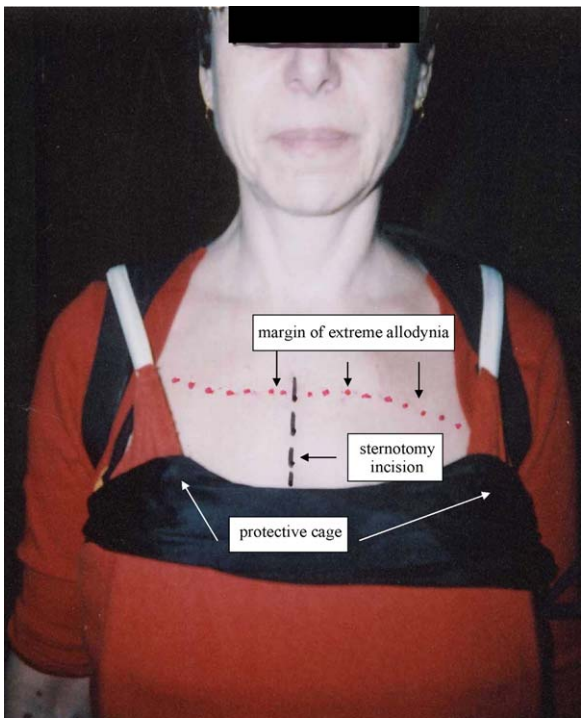

Fig. 5. LB: this woman had extreme dynamic mechanical allodynia after a sternotomy incision for aorto-coronary bypass surgery. Touch of clothing or air blowing on the skin caused severe pain. Note cage protecting her from clothes touching the allodynic skin area. She has been successfully relieved by opioids for 7 years.

Comment: This woman had a catastrophic injury with a severe and intractable pain problem both neuropathic (brachial plexus avulsion) and due to orthopedic injuries to her left knee and spine. Despite major contraindications chronic opioid therapy with careful monitoring has given her a reasonable quality of life for 18 years with stable dosing for 6 years with no indication of tolerance. She continues to be followed regularly and exhibits no signs of drug abuse.

Case 8: LB (Fig. 5) is a 64-year-old female seen 7 years ago regarding severe anterior upper chest pain for 8 months coming on 3 weeks after 4 vessel aorto-coronary bypass with bilateral internal mammary grafting. The main problem was exquisite pain from the touch of clothing or even air blowing on the skin over the sternotomy incision. On examination she had extreme dynamic mechanical allodynia to skin stroking with cotton over 8 cm on each side of the incision with reduced punctate, touch, and pinprick. She had a frame made to wear over her shoulders which kept clothing from touching this area. Otherwise she did not wear a brassiere or clothing over her chest when at home. Gabapentin and amitriptyline provided no relief when titrated to side effects. Transdermal fentanyl (250 morphine equivalents/day) every 3 days reduced steady burning and shock-like pain to 2–4/10 and the allodynia from 10/10 at rest but 4–5/10 with light moving touch with cotton. She reports that pain is 80–90% better, she is able to wear clothing most of the time and has been able to go to work. She has been on the same dose for 6 years.

Comment: A moderate dose of opioid resulted in 7 years of good relief of her inability to wear clothing with good function and no significant side effects in an uncommon and severe NP problem.

Case 9: AC (Fig. 6) is a longstanding diabetic man seen 20 years ago regarding a several month history of severe (10/10) steady aching and burning pain in the femoral nerve territory. This had occurred at the saphenous vein harvest site in the left leg on waking from aorto-coronary bypass surgery. He was considered by his surgeon to have a psychologically based pain problem. The leg was

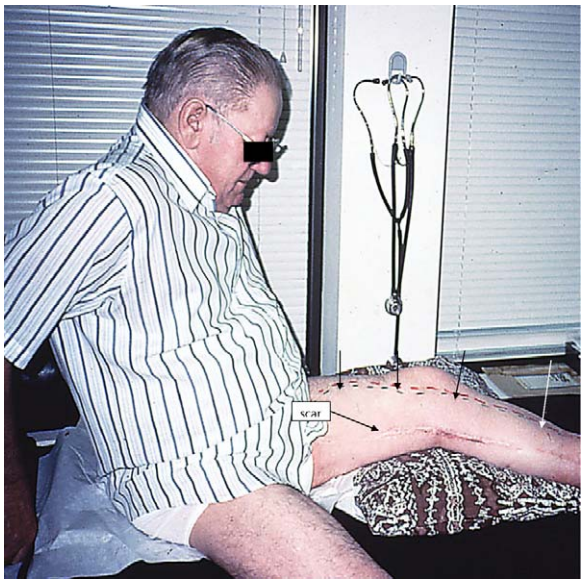

Fig. 6. AC: this man has been on opioids for 20 years, successfully suppressing severe allodynia in an area of sensory loss at the graft harvest site for aorto-coronary bypass surgery. The area of sensory loss is indicated by the black interrupted line. The area of allodynia is indicated by the red interrupted line.

so sensitive to touch that he had cut off the trouser leg on that side. Examination revealed a scar down the medial left leg from thigh to calf. Surrounding this was 5–10 cm of skin exhibiting exquisite dynamic mechanical allodynia with blunting to punctate touch and pin. He was treated with long-acting morphine titrated to 200 mg/day with good relief and pain reduction to 4/10, the dose being the same at 4 years of follow-up. He was able to perform activities of daily living and wear his trousers when up.

Comment: This man has had reasonably good relief for 4 years of an uncommon NP causing severe allodynia with a moderate dose of morphine of the disease specific outcome of the ability to wear clothing.

Case 10: LE (Fig. 7) is a 55-year-old female seen 10 years ago with a 2 year history of glossopharyngeal neuralgia (severe at 10/10) lasting seconds but occurring in bursts and electric shock-like pain in the left pharynx many times a day on swallowing saliva, eating and speaking. Additionally she had idiopathic, severe, steady, burning pain in the in left infraorbital nerve territory with reduced sensation. MRIs were normal. The infra-orbital pain was reduced to 2/10 by transdermal fentanyl (90 mg morphine equivalents/day) every 3 days. The pharyngeal shocks responded only to carbamazepine (CBZ) at 800 mg/day reduced by 50% in frequency but not severity and she elected to have a microvascular decompression operation. After this the pain was completely suppressed by the same dose of carbamazepine. A third problem was her severe and frequent migraine without aura that responded specifically to sumatriptan and the preventive drug flunarizine, a calcium channel blocker. Her migraine became manageable at 2 headaches/month with good relief with the sumatriptan. Good relief (no neuralgia on CBZ, 2/10 left V2 pain on opioid) of all pains persists at 7 years follow-up.

Comment: For this woman an opioid has become part of the management of a complex pain problem the 3 components of which have responded to different drugs over 7 years.

4. Discussion

The case reports discussed here are selected from a published survey [34] based on experience with 84 patients with intractable, severe, disabling CNCP treated with opioids over a median of

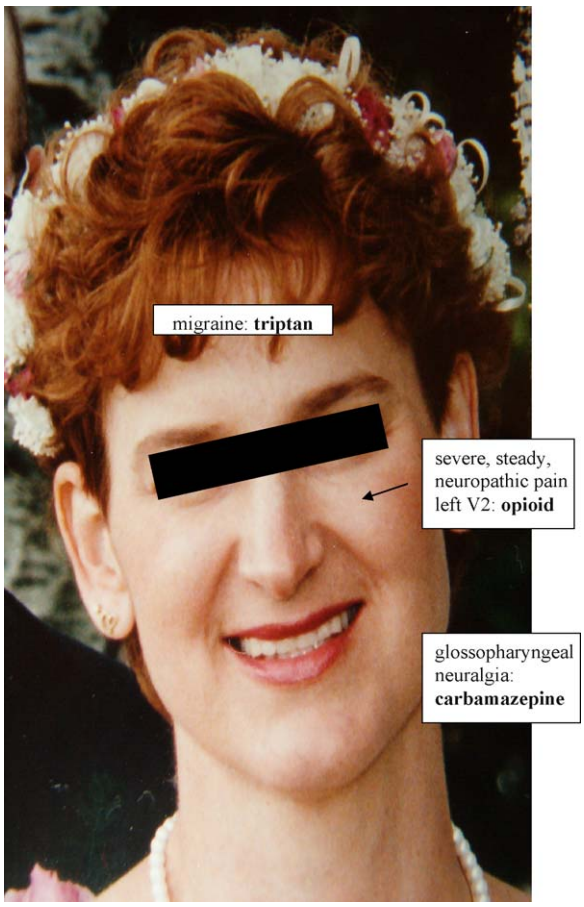

Fig. 7. LE: this patient had a combination of severe migraine treated with a triptan, severe glossopharyngeal neuralgia treated with carbamazepine and microvascular decompression and severe steady neuropathic pain in the maxillary division of the left trigeminal nerve relieved by opioid for 7 years.

8.5 years (up to 2007). We concluded that, in this selected group, opioids were moderately effective and safe in the long term. Most subjects reported at least 50% or greater pain relief and a moderate improvement in disability. Functional status was not severely affected (BPI-I [38] and PDI [39,40] were in the moderate or less range). Two-thirds of subjects were not depressed or anxious by the HADS [41]. Health-related quality of life was not severely affected (SF12v2 [42] only slightly less than normative values). Problematic use, tolerance, and serious adverse effects including constipation were not major problems. Constipation relief was individualized but usually did not require aggressive treatment. In the back and neuropathic leg pain group, which constituted the largest group of 24 patients, the median dose was 510 mg/day. The high dose required in this group may explain the failure of a comparative trial of smaller doses of up to 15–90 mg/day of morphine (versus nortriptyline) in chronic lumbar root pain [43]. The most common opioid used in our survey was oxycodone followed by morphine, transdermal fentanyl and hydromorphone.

It is difficult to conduct an RCT of opioids in CNCP over long periods of time and data in this regard are both observational [29–34] and epidemiological [2–5,35–37]. This selected patient case series report the management details of a variety of CNCP conditions which are, as in the larger group from which they are derived, substantially or moderately relieved with improved functioning and quality of life by a variety of different opioids. The latter were sometimes in high doses, either in monotherapy or in combinations of long and short acting opioids. These CNCP conditions include difficult to treat NP problems but also arthritic and visce-

ral pain. The cases capture issues less available elsewhere such as disease-specific outcomes (ability to wear clothing with neuropathic pain or use a prosthesis in phantom limb pain), combination therapy, concurrent addiction history and long term follow-up. It is important to put a face on these patients in view of the intensity of concern raised by addiction specialists, journalists and the public about the putative abuse and mortality from opioids even in CNCP patients.

RCTs in CNCP conditions such as NP have limitations, seldom exceed 6–12 weeks and 80% have been carried out in painful diabetic neuropathy (PDN) and postherpetic neuralgia (PHN). General guidelines based on these RCTs in these two conditions will likely not be applicable to other and more intractable NP conditions such as spinal cord injury, phantom limb pain, incisional neuralgias (postmastectomy, postthoracotomy) or central post-stroke pain or those with different pain mechanisms. Negative trials of opioids and nortriptyline in sciatica [43] and amitriptyline in HIV neuropathy are examples [48]. As well, these results may not be applicable to uncommon NP conditions which, because of their scarcity, are not amenable to RCTs such as anesthesia dolorosa, causalgia, brachial plexus avulsion, syringomyelia and others. RCTs will likely not be feasible with complex patients having multiple pain components requiring two or more drugs because of the complexity of study design and length of time required because of the number of treatment arms, the need for washout periods and carry over and natural history effects in the commonly-used crossover designs in this area of research. Additionally, in our experience, it is becoming harder to generate suitable patients for RCTs because of the moderate success of such drugs as gabapentinoids and antidepressants in primary care.

It is likely that the favorable impact of these drugs in specific pain problems in individuals and in the long term may not be captured by observational and epidemiological data. Functional outcome measures such as the BPI-I and PDI are not disease-specific and when used in RCTs or observational studies will not capture improvements such as the ability to tolerate clothing with allodynia relief (cases 8 and 9), improvement in eating (case 3), wearing of a prosthesis after amputation (case 1), or, in other conditions, tolerance of the light touch of clothing (allodynia) with postmastectomy syndrome and postherpetic neuralgia.

Silas Weir Mitchell, arguably the most famous neurologist in North America in the 19th century, wrote from his American civil war experience that, "For the easing of neurotraumatic pain we tried in turn the whole range of medicines and none of them, save morphia, seemed to be the slightest value. . .the morphia salts are invaluable" [49]. Because of the widespread availability of opioids in patent medicines without prescription, and recommendations such as that of William Hammond, the surgeon general of the army at that time, to add cocaine to wine as a tonic, there arose a major problem leading to opioid phobia generated by the availability and liberal use of opioids. This persisted until the mid 20th century when the hospice movement demonstrated the utility of oral morphine for cancer pain. This experience gradually penetrated the treatment of CNCP in refractory cases. Perhaps we now have an analogous situation where opioids are in widespread use and readily available to those who would abuse and divert them. Inadequate education of prescribers has produced an excessively liberal use with inadequate screening and selection of patients, inappropriate use and limited follow-up.

Several RCTs indicate that opioids relieve NP in the short-term which constitutes a substantial portion of CNCP [12–20]. These data indicate that drugs such as oxycodone relieve steady burning, shock-like pain and skin sensitivity in PHN and PDN as well as improve the quality of life [12,17].

There are a number of observational long-term studies in the literature [29–34]. Previous observational studies have indicated that opioids may be effective long-term [29,32,33] but some caution about the lack of functional improvement and have raised concern about the abuse potential of these drugs [30,31]. Epidemiological studies have suggested problems with long-term use including a low health-related quality of life [4,5,35–37]. A conclusion was that opioid use did not fulfill outcomes of relief, health-related quality of life, and functional capacity. Toblin et al. reported similar results in the American state of Kansas regarding the association of opioid use with poor health outcomes [5]. However, Sjogren [2,4] concluded that "the Danish surveys and the Toblin et al. study demonstrate the limitations of cross-sectional data that attempt to assess the consequences of the extensive and liberal use of opioids in CNCP".

An opioid treatment guideline [44] has concluded that the evidence for the use of opioids in CNCP is limited, that the evidence for screening tools predicting addiction is also limited, and that clinical decisions regarding the use of opioids in CNCP need to be made based on weak evidence. They also state that there is some evidence that opioids are effective for some patients with CNCP.

On the basis of the different views from addiction medicine, epidemiology, journalists and the law, it may be, as in the folktale of the blind men and the elephant; that we each have a different piece of this beast and are coming to different conclusions.

The strength of observational data such as these case reports is the identification of a population of complex patients, with intractable pain, who benefit from opioids over the long-term and often in disease-specific ways. These data capture information that may be inaccessible to RCTs of monotherapy or even of combination therapy in selected patients over the short term and by other observational and epidemiological data. Despite having good internal validity, RCTs may not address real world contexts. The limitation is that these data may not be generalizable to a larger population because of the probable selection of patients who benefit and who do not have intolerable adverse effects. The bias of subject and observer is always a factor in non-blinded studies. It is possible that some of our patients are abusing or diverting opioids but trust is essential as well as careful screening and follow-up and there has been minimal evidence of this over many years except for 12 instances (one of diversion, 11 of abuse) over 30 years in patients with a known addiction history given an opioid trial because of a severe concomitant chronic pain condition. All were discharged except one (case 7, RL), who, after treatment of bipolar disorder has not been a problem for 16 years. These problematic patients were all recorded from a population followed over many years. This group averaged between 80 and 100 patients at any one time with some flux but there may be others with problematic use who were lost to follow-up.

5. Conclusions

Opioids appear safe and moderately effective for selected patients with CNCP most of whom had NP. High doses of opioids are sometimes required. Escalating doses of opioids have not been problematic, as beyond a certain plateau, with reasonable relief, more pain relief did not occur with further dose increases. Refractory constipation and other side-effects have also been uncommon. These data provide evidence of an improvement in quality of life and physical functioning, sometimes disease-specific, of a moderate degree predominantly in a change from being bedridden to being able ability to perform activities of daily living. It is not realistic for many patients to have complete relief or even a reduction to mild pain. However, often a change from severe to moderate or less severe even without any change in function is a great improvement for many sufferers and an acceptable outcome in their view.

Of course, great care must be taken with this practice. Detailed guidelines are available [50]. Simplified pragmatic guidelines are feasible:

- prescribers must have adequate education in this area,
- screening of potential patients is critical (as with the screener and assessment for patients with pain (SOAPP-R) [45] and the opioid risk tool (ORT) [46]),
- it is prudent to have a verbal or written contract with patients regarding rules to be followed with these drugs (one prescriber and pharmacy, secure drug location),
- documentation is essential (drug and dose, pain severity, relief, adverse effects, functional status, quality of life, mood, physical findings) at each visit,
- regular follow-up with prescription copies and charting is prudent (our Ontario regulatory body's attitude is that if it is not documented you did not do it!),
- ideally patients who may require vigilance (doses > 200 mg morphine equivalents/day) are possibly best managed by a pain clinic or pain specialist,
- if indicated opioid withdrawal should be gradual to avoid physical withdrawal symptoms.

Further information is required about patient selection as to whom we should treat and whom we should not treat. Patients should have moderate to severe pain with adequate trials of non-opioids and those with refractory NP, visceral and arthritic pain are suitable. Patients with fibromyalgia and myofascial pain as well as most chronic headaches are, in our opinion, usually not good candidates for opioid treatment. Further data are needed as to the utility of screening tools regarding the potential for problematic opioid use. As well, further long-term observational data are needed to capture the impact of this approach for those patients with CNCP for whom all other approaches have been exhausted.

In summary the case reports here document the benefit of opioids often in high doses for very severe and intractable CNCP. Even with these powerful drugs the results can be less than optimal, although significant to the sufferer. A great issue in the treatment of CNCP is the limited efficacy for many of our patients of all drugs and non-pharmacological approaches in monotherapy or in combination. We sorely need new ideas about mechanisms, how to use best our existing remedies and novel treatment approaches.

And so these wise men
Disputed loud and long
Each in his own opinion
Exceeding stiff and strong
Though each of them was partly right
And each was partly wrong.

Folk tale: The Blind Men and the Elephant

Conflict of interest

The author has no conflict of interest regarding this article.

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