

Intrathecal Fentanyl for Chronic NonMalignant Pain

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Intrathecal Fentanyl for Chronic Nonmalignant Pain.

Background

The administration of opioid therapy for the management of pain in patients with terminal cancer is a generally accepted practice⁽¹⁾. The identification of opiate receptors in nervous tissue in the 1970's revealed the potential for opiate intrathecal drug delivery. Several years later, the opiate receptor was identified in spinal cord parenchyma. In 1979, intrathecal administration of morphine was first reported to provide substantial relief of pain in cancer patients⁽²⁾. At present, morphine remains the opioid of choice, as recommended by the World Health Organization, for the management of moderate to severe cancer-related pain⁽¹⁾.

Even though oral and intravenous routes of opioid administration are widely used, the systemic side effects of opioids often limit their use⁽³⁾. First introduced in the mid 70's, intrathecal opioid use was hypothesized to circumvent those side effects associated with high dose systemic opioids. It was thought that intrathecal opioid use would deliver the drug molecules to or near the site of action within the spinal cord and bypass the blood brain barrier, thus reducing the amount of opioid needed to obtain a similar clinical effect as that delivered orally at much higher doses. Intrathecal and epidural use of morphine expanded rapidly during the 1980's and 1990's. The US FDA (Food and Drug Administration) sanctioned the use of continuous non-programmable infusion pumps for the administration of morphine. In 1991, the programmable Medtronic Syncromed system was approved by the US FDA⁽²⁾. Despite the fact that the intrathecal administration of opioids was initially approved for pain control in cancer patients, it is now widely used in chronic non-cancer pain patients, including those individuals with failed back surgery⁽⁴⁾.

Fentanyl, a derivative of phenylpiperidine, is a synthetic opioid which was introduced into clinical practice in 1960^(3,5,6). Like morphine, fentanyl is a μ receptor opioid. Compared to morphine, however, fentanyl has a lower molecular weight, is 75 - 100 times more potent and is approximately 1000 times more lipid soluble than morphine. However, the enteral (oral administration route) bioavailability of fentanyl is poor. Because of this, the usual routes of administration of fentanyl are parenteral, including intravenous, spinal, subcutaneous, transdermal and transmucosal^(3,5,6).

Objective

The objective of this short review is to investigate the effectiveness of intrathecal fentanyl in treating chronic nonmalignant pain patients. The review will place an emphasis on intrathecal fentanyl use in patients with unsuccessful back surgery.

Materials and method

A systematic review on intrathecal fentanyl for chronic nonmalignant pain was undertaken.

Literature searches were undertaken on medical literature databases including PubMed, Cochrane Library, Bandolier, the US Agency for Healthcare Research and Quality, the NHS Centre for Reviews and Dissemination at the University of York and websites of members of the International Network of Agencies for Health Technologies Assessment (including Canada, the US including the Department of Veterans Affairs and Blue Cross/Blue Shields TEC Assessment, Great Britain, New Zealand, Australia, Sweden and Denmark). The search was conducted on the websites of several private health insurers (including Aetna, Blue Cross of California, Humana, Permanente Medical group, Tuft and Western Health Advantage), in order to identify their reimbursement policies on intrathecal drugs for chronic pain.

The search was undertaken in order to identify published systematic reviews, randomized/controlled trials or any other study designs including case-series/reports on treatment of chronic nonmalignant pain patients with intrathecal fentanyl. This search was done by employing a combination of medical subject heading and keywords of: continuous intrathecal fentanyl, intrathecal fentanyl pump, intrathecal morphine pump, continuous intrathecal morphine, intrathecal morphine, chronic pain, chronic non-malignant pain, failed back surgery/surgeries. The word intrathecal was also substituted by subarachnoid. The searched was done up to February 2005.

- *Inclusion criteria:* publications were selected for critical review if they involved human adult subjects. There was no restriction placed on the year of publication.
- *Exclusion criteria:* publications were restricted to those where at least the abstract was available in English. Publications on intraspinal fentanyl or morphine without additional clarification, whether it was epidural or intrathecal, were also excluded. Systematic review/review articles were excluded if the methodology used to evaluate the quality of the primary studies were not apparent

Appendix 1 provides the interpretation of level of evidence as adopted by the Evidence Based Practice Group at the WCB of BC.

Results.

- Systematic reviews (Level 1 evidence)

1. Bennet et al⁽⁶⁾ published a systematic review on intrathecal delivery of pain medications. Even though the search was limited to Medline database (1966 - October 1999), the search was done thoroughly by employing 12 different search strategies with numerous combinations of keywords (including 'long term'). This electronic search was then followed by manual citation list searches. By employing various combinations of these search strategies, the authors developed a review on 21 drugs or drug combinations for treating chronic pain

via intrathecal or epidural administration, including opioids, local anaesthetics, adrenergic agonists, N-Methyl-D-Aspartate antagonists and other agents including somatostatin analogs. There were no further inclusion/exclusion criteria specified. The authors did not mention the number of researchers assigned to critically-appraise the manuscripts retrieved for this systematic review. However, information was abstracted uniformly by employing a standardized data retrieval form.

With regard to fentanyl, the authors concluded that, even though the use of intraspinal fentanyl had been reportedly extensively, there were no randomized controlled trials on the use of epidural or intrathecal fentanyl. There were three retrospective case series on the efficacy of 'long term' intrathecal fentanyl. The largest of these described 551 patients treated for lower back pain with continuous epidural infusion of a combination of bupivacaine/fentanyl/droperidol (not fentanyl alone). Most were treated via an external pump system. A small number were treated with an implanted pump. The majority of the patients received an infusion of 2 ml/hr containing fentanyl 5 mcg/ml, bupivacaine 9mg/ml and droperidol 0.05 mcg/ml. The infusion was repeated between 2-9 times (mean 7 times) over a mean duration of 19.8 days (range 2 - 81 days). Time between infusions ranged from 6 - 184 days (mean 12 days). Pain relief was reported to be excellent in 73% and good in 26.5%. No serious side effects were noted. Bennet et al⁽⁶⁾ did not provide a summary on the characteristics of patients included in these case series.

The same author concluded that clinical efficacy in large scale randomized controlled trials utilizing intrathecal delivery of most compounds, including fentanyl, had not been demonstrated. Further, variations in term of study designs, patient characteristics, differences in either single or combinations of drugs being employed and inconsistent outcome criteria being measured made it difficult to draw significant conclusions. Data on drug interactions, long term safety and toxicity were also lacking.

2. Kalso⁽²³⁾ undertook a systematic review on the effectiveness of opioids in treating chronic noncancer pain. The author did a comprehensive electronic search (up to May 2002) on various databases including Medline, Cochrane Library, EMBASE and the Oxford Pain Relief Database followed by a manual search in order to identify randomized controlled trials (RCTs) of fentanyl, hydromorphone, methadone, morphine, oxycodone and oxymorphone use in treating noncancer pain. The author found 13 RCTs. Four were on intravenous opioid testing and nine were on oral opioid use. The author did not report on any intraspinal opioid use or treatments.
3. Ribeiro and Zeppetella⁽⁵⁾ posted a protocol on the Cochrane Library for systematic review on 'Fentanyl for Chronic Pain'. This protocol has been posted in the Cochrane Library for longer than two years without substantive amendment. It should be noted that one of the Cochrane Library policies is that a protocol listed for longer than 2 years without substantive amendment should be withdrawn. To date, this has not happened.

- **Randomized/controlled trials (Level 1 evidence)**

We have failed to identify any published literature (up to January 2004) of randomized/controlled trials on the effectiveness of intrathecal fentanyl in treating chronic nonmalignant pain due to failed back surgery. Further, there appeared to be no published literature on randomized/controlled trials on the effectiveness of intrathecal fentanyl in treating chronic nonmalignant pain in general. The majority of published literature in the area of chronic nonmalignant pain treatment focused on the application of intrathecal morphine instead of fentanyl. Most of these studies were case series/reports type of study designs (Level 4 evidence). **Thus, the majority of published literature being employed in this review relate to intrathecal morphine instead of fentanyl. (See below).**

- **Case series (Level 4 evidence)**

Table 1 summarizes the available case series on long term intrathecal morphine for treating chronic nonmalignant pain. The studies were done among adults and elderly males and females. All of these studies involved patients with failed back surgery. These studies suggest that there may be some low level evidence on the effectiveness of intrathecal morphine in the long term treatment of chronic nonmalignant pain. However, the evidence is still inconclusive due to the variability in outcome criteria/measurement tools, follow-up periods and the supplemental use of other analgesics, antidepressants or sedatives. It is of interest that some of these studies demonstrate dose escalation of up to 20 times, from the start of the trial to the end of the follow-up period.

- **Surveys and non systematic reviews (Level 4 evidence)**

Dahm et al⁽⁹⁾ published a non systematic review on the efficacy and technical complications of long term intraspinal infusions of opioids with or without local anaesthetics (bupivacaine) in refractory nonmalignant pain. The authors did not mention the databases searched, nor did they mention any inclusion/exclusion criteria for the literature search, nor the time frame of the review. There were 21 studies (12 used an epidural approach and 9 used an intrathecal system, both with external or implanted catheters) found on intraspinal infusions of opioid with or without local anaesthetics (bupivacaine) in refractory nonmalignant pain. The authors concluded that 88% of patients treated with intrathecal morphine had satisfactory pain relief (defined as pain reduction \geq 40%).

Paice et al⁽¹¹⁾ conducted a survey among physicians in the United States who had implanted > 5 SynchroMed® pumps. Seventy physicians (neurosurgeons, anesthesiologists, orthopedists and others) met the inclusion criteria defined in the study. There was a 50% physician response to the survey. 819 patients of these 35 physicians were subsequently surveyed. 429 (52.4%) patient surveys were returned. Of the 429 returned patient surveys, permission was given to contact 131 (29%) of these patients. 67.2% of the 429 patients had chronic nonmalignant pain. Among the 429 patients, the most common diagnosis was failed back surgery (42.4%), followed by cancer (31.0%). The mean initial morphine dose for

nonmalignant cases was 2.0 mg/day. The mean morphine dose at 24 months follow-up was approximately 14 mg/day.

- Chronic nonmalignant pain patients - selection criteria for intrathecal morphine (or fentanyl) use

The patient selection criteria being used by various case-series, expert reviews or clinical guidelines are summarized in Table 1. Of six case series reported in Table 2, only one (reference no. 14) reported the application of intrathecal fentanyl among eight patients with chronic nonmalignant pain.

The following is a summary of some of the selection criteria:

- Intrathecal morphine for the management of chronic nonmalignant pain patients was used in adults only without regard to gender.
- Intrathecal morphine was used in many diseases with minimal to severe level of chronic nonmalignant pain being a major indication. Failed back surgery was a common diagnosis.
- Some studies suggested that intrathecal morphine was more effective for neuropathic or mixed types of pain syndromes.
- Synchronmed pumps from Medtronic were implanted in the majority of the studies summarized.
- Prior to an intrathecal morphine trial, oral opioids and other less invasive pain controls therapeutic maneuvers had been tried and failed. The less invasive pain control modalities included TENS, nerve blocks, acupuncture, hypnosis, spinal cord stimulators and even placebo.
- Candidates for intrathecal morphine trials were generally excluded if they had a history of substance abuse. Many patients also underwent a psychiatric review. One study⁽¹⁴⁾ (from Saskatchewan) limited their candidates to those patients without medicolegal issues.
- All of the studies suggested a trial of intrathecal morphine (given either as a bolus injection or continuous infusion) prior to any permanent implantation. The majority of these studies suggested that at least a 50% reduction in pain (measured by various methods include a subjective visual analogue pain level before and after trial) during the trial as a minimum threshold before proceeding to permanent implantation.
- Notice that the majority of these studies suggested that patients still received additional systemic analgesics/opioids or other medications while receiving the intrathecal morphine. .

Regardless of the patient selection criteria, none of these studies provides a 100% success rate (based on different outcome measurement tools). As such, it can be concluded that patient selection criteria for intrathecal morphine (and likely, therefore, fentanyl) use is still unclear. Further, (and this bears special comment), the majority of patients on intrathecal morphine still received additional systemic analgesics/opioids.

- Published adverse events on long term treatment with intrathecal morphine

Adverse events related to intrathecal morphine treatment can be due to the pharmacological side effects of morphine, complications of surgery and/or device related complications.

Table 2 (2nd page) provides a summary of adverse events recorded in case series studies on intrathecal morphine. The majority of these adverse events involved the pharmacological side effects of morphine which usually developed early on in the course of treatment, and were transient in nature. These adverse events included nausea, pruritus, disturbance in micturition, diaphoresis and others. Serious adverse events that potentially required surgical treatment usually involved the delivery systems, including catheter migration, catheter obstruction and pump malfunction. The incidences of these serious adverse events varied from 10% to 33%. The development of morphine tolerance was also noted in one of the studies⁽¹³⁾.

In their survey among physicians, Paice et al⁽¹¹⁾ reported delivery system complications in 82 patients (21.6%). The most common pharmacological side effects reported in this survey was nausea and vomiting (25.2%), edema (11.7%), diaphoresis (7.2%), weakness (7.2%) weight gain (5.4%) and diminished libido (4.9%). Paice et al⁽²⁴⁾ also noted that cauda equina syndrome secondary to the implantation was very rare. Over a 50-year period of intraspinal treatment, there have been only 22 reports of this surgical emergency syndrome in the literature.

As part of a 16-centre phase III study of intrathecal administration of a new compound, Medtronic, the producer of SynchroMed®, recorded in its database that catheter failure ranged from 6% to 60%⁽²⁾.

Serious adverse events related to intrathecal morphine also include respiratory depression. In a non systematic review, Gilmer-Hill et al⁽²⁵⁾ noted that the incidence of respiratory depression due to intrathecal morphine use is < 1%.

Another rare but serious adverse event related to intrathecal morphine is the development of an inflammatory mass on the tip of the catheter⁽²⁶⁻²⁹⁾. To date, 41 cases have been identified⁽²⁶⁾, 16 from the medical literature and 25 from the US FDA adverse effect report database. In all cases, the inflammatory mass was found to be at the level of the catheter tip. The mass, which on average took two years to develop, produced signs and symptoms of spinal cord injury. The development of these inflammatory masses at the tip of the catheter was usually associated with high dose opioid use⁽²⁶⁾. Coffey and Burchiel⁽²⁶⁾ hypothesized that the development of the inflammatory mass was associated with either high dose application of opioids or was due to the application of drugs or mixtures of drugs that were not labeled for intrathecal use.

- Economic studies on intrathecal opioids

There were two published studies, one from the US⁽¹⁹⁾ and one from Saskatchewan, Canada⁽²⁰⁾ on the economic analysis of intrathecal drug therapy.

1. Lissovoy et al⁽¹⁹⁾ published a comprehensive, methodologically sound Monte Carlo simulation on the cost effectiveness of long term intrathecal morphine therapy for pain due to failed back surgery.

The objective of this study was to estimate the direct cost (i.e. from the insurer's point of view) of intrathecal morphine therapy delivered through implantable pumps relative to alternative modalities (anything, including repeat back surgery) during a 60-month period of treatment. Probability numbers (including number of various treatment modalities and number of adverse events) needed to construct the Monte Carlo simulation were undertaken based on the available published literature on the issue of intrathecal morphine therapy due to failed back surgery. When there was a lack of data on the probability of certain events, the number was then approximated or substituted by the numbers taken from intrathecal morphine treatment studies among cancer patients.

The authors suggested that with both adverse events and costs set at the most likely values, the estimated 60 months total cost of intrathecal morphine for treating failed back surgery was US \$ 82,893 - an average of US \$1,382 per month (the value is based on 1996 US dollar, discounted at 5% per annum). Based on sensitivity analysis, the authors estimated that the cost of intrathecal morphine treatment was between US \$53,468 (US \$891/month) to US \$125,102 (US \$2085/month) when the probabilities of adverse events and costs were set at the lowest and at the highest possible, respectively. Estimated cost-effectiveness values ranged from US \$7,212 (best case) to US \$ 12,276 (worst case) per annum of pain relief.

Based on computer simulation results, the intrathecal morphine treatment for failed back surgery appeared to be cost-effective when compared with alternative treatments for selected patients when the duration of therapy exceeded 12 to 22 months. It should be noted that the estimated life of the pump is between 48-60 months.

Even though this study is very sound methodologically, we need to advise that the results should be interpreted with caution. This is due to the fact that, even though the cost data was valid, the probability numbers employed and the effectiveness data come from case series studies instead of randomized controlled trials.

2. Kumar et al⁽²⁰⁾ from Saskatchewan published a 'cost-effectiveness analysis' on the treatment of chronic pain by using intrathecal drugs compared to conventional pain therapies.

Eighty-eight chronic pain patients due to failed back surgery, (who failed to achieve adequate treatment relief with spinal cord stimulators) were recruited for this study. Forty-four patients were assigned to the intrathecal morphine pump arm (23 patients eventually received a permanent implant) and 44 were assigned to other chronic pain treatment modalities (i.e. non intrathecal morphine arm of the trial). The assignment was done 'randomly' and was 'matched' on age, sex and the number of operations undergone [Note: it is impossible methodologically to do a random assignment and matching at the same time. By definition, random assignment will negate the possibility of matching (interventions with the controls) which has to be done not at random.] This alone likely negates any conclusions from this study.

The 21 patients (of 44 patients in the intrathecal group), who did not receive permanent intrathecal pump implantation, were not included in the cost calculation of the intrathecal group [Note: not analyzing according to the 'intent to treat' principle, breaks all randomization procedure rules.] Thus, there were 67 patients followed for five years.

The authors included direct cost from the insurer's point of view by employing the Saskatchewan Medical Practice fee schedule. The authors concluded that the actual cumulative costs for intrathecal drug treatment during a five-year period was Can \$ 29,410 as compared to Can \$ 38,000 for other modalities of pain treatment. High initial costs of equipment required for intrathecal drug treatments were recovered in 28 months.

The authors also presented data on the Oswestry Disability Index. The Oswestry Disability Index showed 27% improvement for patients in the intrathecal group as compared to 12% improvement in the other treatment group.

The authors concluded that intrathecal morphine was cost effective in the long term treatment of chronic nonmalignant pain despite high up front costs due to the devices. However, the results and conclusions of this study must be interpreted very cautiously. There are major flaws in the design of this study, namely the contradiction of randomization with matching, and the cost calculation that did not include those who did not get a permanent intrathecal pump.

- Who is paying for intrathecal pumps?

In their respective medical policy bulletins, AETNA⁽²¹⁾ and Blue Cross of California⁽²²⁾ explicitly state that the insurance companies provide reimbursement for implantable infusion pumps, including intrathecal pumps for drug delivery.

Summary.

- Currently, the US FDA only approves morphine and baclofen for intrathecal use. However, other opioids are used for intrathecal delivery in a variety of clinical settings for pain management (acute or chronic, short or long term)⁽¹⁷⁾.
- In their survey of clinical trends and decision making in intraspinal therapy, Hassenbusch et al demonstrated that large variations between practitioners were evident in the management of chronic nociceptive and neuropathic pain patients.
- To date, there is a paucity of published literature on the effectiveness of intrathecal fentanyl in treating nonmalignant chronic pain patients.
- Level 4 evidence (See Appendix 2) did suggest some positive evidence on the effectiveness of intrathecal morphine in treating chronic nonmalignant pain. However, studies also showed that:
 1. there was no patient selection criteria that guaranteed a high level of success of the treatment;
 2. the use of intrathecal morphine was associated with a high incidence of side effects related to the drug itself, the drug delivery vehicles and the complications of surgery;
 3. chronic nonmalignant pain patients treated with intrathecal morphine were usually also prescribed other analgesics, antidepressants and/or even oral opioids at the same time;
 4. the cost effectiveness studies done on intrathecal morphine did not provide definitive evidence on its cost effectiveness due to the paucity of relevant data necessary to construct such a study. Methodological concerns around the one published study on cost effectiveness likely negate any of its conclusions.

Appendix 1

Workers' Compensation Board of B.C. – Evidence-Based Practice Group. Quality of evidence ^(adapted from 1,2,3,4)

Quality of Published Evidence

1	Evidence from at least 1 properly randomized controlled trial (RCT) or systematic reviews of RCTs.
2	Evidence from well-designed controlled trials without randomization or systematic reviews of observational studies.
3	Evidence from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group.
4	Evidence from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments could also be included here.
5	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

Reference

- ¹ Canadian Task Force on the Periodic Health Examination: The periodic health examination. CMAJ. 1979;121:1193-1254.
- ² Houston TP, Elster AB, Davis RM et al. The US Preventive Services Task Force Guide to Clinical Preventive Services, Second Edition. MA Council on Scientific Affairs. American Journal of Preventive Medicine. May 1998;14(4):374-376.
- ³ Scottish Intercollegiate Guidelines Network (2001). SIGN 50: a guideline developers' handbook. SIGN. Edinburgh.
- ⁴ Canadian Task Force on Preventive Health Care. New grades for recommendations from the Canadian Task Force on Preventive Health Care. CMAJ. Aug 5, 2003;169(3):207-208.

Table 1. Summary of published case series on intrathecal fentanyl or morphine for chronic nonmalignant pain.

Reference no. Study summary	7	10	12	13	14	15
Participants	<ul style="list-style-type: none"> - 11 patients - 5 males, 6 females - Age 29-81 years - 9 (82%) due to FBS 	<ul style="list-style-type: none"> - 90 patients - 40 males, 50 females - Age 20-96 years - 3 (3%) due to FBS 	<ul style="list-style-type: none"> - 120 patients - 60 males, 60 females - Age 28-79 years - 73 (61%) due to FBS 	<ul style="list-style-type: none"> - 30 patients - 14 males, 16 females - Age 35-83 years - 14 (47%) due to FBS 	<ul style="list-style-type: none"> - 16 patients - 10 males, 6 females - Age 34-61 years - 8 (50%) due to FBS 	<ul style="list-style-type: none"> - 12 patients - 7 males, 5 females - Age 34-68 years - 11 (92%) due to FBS
Study period	Febr 1992 - July 1995	Febr 1987 - Dec 1995	July 1988-Nov 1993	Not available	Not available	Not available
Interventions	<ul style="list-style-type: none"> - IT morphine - Initial dosage 0.125 - 0.750 mg/day 	<ul style="list-style-type: none"> - Either IT morphine, buprenorphine and or bupivacaine - Initial dosage of morphine 0.1 mg/hr, buprenorphine 0.03 mg/hr, bupivacaine 1mg/hr - Ad lib spinal bolus doses & other analgesics 	<ul style="list-style-type: none"> - IT morphine or buprenorphine - Mean initial dosage of morphine 2.7 mg/24hrs - Ad lib oral sedative and analgesics 	<ul style="list-style-type: none"> - IT morphine or hydromorphone or morphine + bupivacaine - Mean initial equianalgesic dosage 1.96 mg/day - Ad lib oral non-opioid analgesics 	<ul style="list-style-type: none"> -IT morphine or morphine+clonidine - Mean initial morphine dosage 1.11 mg/day - Ad lib oral narcotic, antidepressant and or analgesics 	<ul style="list-style-type: none"> - IT morphine - Mean initial morphine dosage 0.88 mg/day - Ad lib oral analgesics
Outcomes	<ul style="list-style-type: none"> - follow-up period 7-39 months, mean 27 month - 8 (73%) had well to excellent pain reduction (include 6 (67%) of FBS). 3 (33%) other FBS analgesic responses were judged poor. No clear criteria for good or bad analgesic outcome - End of follow-up morphine dosage 1.5-14 mg/day 	<ul style="list-style-type: none"> - Follow-up period 3 - 1706 days (median 60 days) - 86 (96%) achieved 60%-100% pain relief. Nocturnal sleep duration increased by 4-7 hrs (median). No changed in gait & ambulatory pattern - Reduction on oral morphine by 1/5 (median 30 to 6 mg) - End of follow-up mean morphine dose 0.1-25 mg/day 	<ul style="list-style-type: none"> - Follow-up period 6-68 months, mean 41 months - Mean subjective pain reduction (VAS) 58% - 92% satisfied with the therapy - 81% reported improvement in QoL (no tool used) - Mean follow-up dosage 4.7 mg/day - 31 (26%) cases were considered treatment failures due to insufficient reduction of pain, intolerable side effects or opioid resistance 	<ul style="list-style-type: none"> - Follow-up period 24 months (for 20 patients only) - 8 (40%) had pain relief \geq 50% - Mean follow-up equianalgesic dosage 14.59 mg/day 	<ul style="list-style-type: none"> - Follow-up period 13-49 months, mean 29 months - Mean subjective pain reduction (VAS) 57.5% - 7 patients changed their activity levels from passive or very restricted to slightly restricted - End of follow-up mean morphine dose 7.42 mg/day 	<ul style="list-style-type: none"> - Follow-up period 12 months - Mean 42% reduction in McGill's Pain Questionnaire - Mean 36% reduction in present pain intensity - Mean 35% reduction in hardship of pain - End of 12 months follow-up mean morphine dose 2.18 mg/day

FBS = failed back surgery IT = intrathecal

Table 1. Summary of published case series on intrathecal fentanyl or morphine for chronic nonmalignant pain. Continued.

Reference no. Study summary	7	10	12	13	14	15
Adverse events:	<ul style="list-style-type: none"> - 3 (27%) had nausea - 2 (18%) had pruritus - 2 (18%) had urinary retention 	<ul style="list-style-type: none"> - 17 (19%) had opioid withdrawal - 3 (3%) had clonus - 3 (3%) had transient hallucinations - 2 (2%) constipation - 18 (%) had nausea/emesis - 1 (1%) had pruritus - 1 (1%) had bradypnea - 33% had transient paresthesia - 22% had transient paresis - 10% had episodic arterial hypotension - 47% transient urinary retention - 3% transient urine incontinence - 1% transient fecal incontinence - 4 (4%) meningitis 	<ul style="list-style-type: none"> - 25 (21%) pumps had to be removed - 16% had <u>no</u> adverse events - 50% had constipation - 43% had disturbance of micturation - 27% had disturbance of potency - 24% had vomiting - 23% had nightmare - 15% had pruritus - 9% had sweating - 6% had edema - 5% had disturbance of libido - 4% each had dry mouth and fatigue - 2.4% each had amenorrhea, dizziness, hypothyroidism - 1.2% each had cerebral convulsion, loss of appetite, provocation of asthma 	<ul style="list-style-type: none"> - 2 (10%) catheter migration from intrathecal space - 1 (5%) catheter obstruction - 2 (10%) CSF seroma development - These 5 patients needed re-operation - 2 (10%) pump malfunction - 1 (5%) pump programming error <p>During 1st 3 months:</p> <ul style="list-style-type: none"> - 31% had constipation - 21% had nausea - 14% lethargic - 14% pruritus - 10% sweating - 3% had disturbance of micturation - 3% had peripheral edema - 3% had escalating pain - 30% developed morphine tolerance (defined as IT morphine dose > 25 mg/day) 	<ul style="list-style-type: none"> - 2 (12.5%) pumps explanted due to intolerable side effects - 1 (6%) pump had to be replaced, - 1 (6%) had local infection - 1 (6%) reoperated due to disconnected catheter - 78% had fatigue - 70% had sweating - 62% each had loss of appetite, constipation, disturbance of micturation, dizziness - 55% had pruritus - 58% each had depression, edema, nausea, myoclonic jerk - 40% each had nightmare, disturbance of libido - 32% each had dry mouth, hallucination - 25% had insomnia - 15% had provocation of asthma - 8% had disturbance of potency 	<ul style="list-style-type: none"> - 10 (83.3%) had at least 1 adverse effects, including: - 6 (50%) had nausea - 5 (42%) had pruritus - 4 (33%) had urinary retention - 4 (33%) had pump related adverse effects, including pocket infection, pocket dehiscence, lumbar wound dehiscence and LCSF leakage
Note:	Did not mention any patient selection criteria	-	- 1 case was changed to fentanyl due to side effects of morphine			this study was a part of a multicentre study on the effectiveness of Infusaid®

• FBS = failed back surgery ** IT = intrathecal

• **Table 2. Patient selection criteria for intrathecal morphine or fentanyl for chronic nonmalignant pain.**

Reference no.	4	7	8	10	11	12	13	14	15
Criteria									
Study design	Guidelines	Case series	Expert	Case series	Survey	Case series	Case series	Case series	Case series
Number of cases recruited	-	Unknown	-	Unknown	429	120	40	25	Unknown
Age (years)	-	29-81	-	20-96	18-91	28-79	35-83	34-61	34-68
Sex:							unknown		
• Male	-	5/11	-	40/90	193/414	60/120	-	6/16	7/12
• Female	-	6/11	-	50/90	221/414	60/120	-	10/16	5/12
Patients with failed back surgery	-	9/11	-	3/90	182/429	73/120	19/40	8/16	11/12
Intrathecal drugs given*	-	M	-	M, B	M, other	M	M, B	M, other	M
Pump type*	-	Synch	-	Pharmacia	Synch	-	Synch	Synch	Synch, Infus
Pain type:									
• Nociceptive	-	-	-	9/90	61/363	13/120	1/30	4/16	1/12
• Neuropathic	-	2/11	-	17/90	137/363	7/1220	10/30	3/16	-
• Mixed	-	9/11	-	64/90	29/363	73/1220	15/30	8/16	11/12
• Other (visceral, deafferentation)	-	-	-	-	136/363	27/120	4/30	1/16	-
Previous oral opioid ?	√	√	√	√	√	√	√	√	√
Previous oral opioid effective ?	No	No	Some	Some	Some	No	Some	No	Some
Replacement for oral opioid due to SE	-	-	√	√	Some	-	-	-	-
Previous treatments failure, such as:	Unknown		Unknown	√	√	√	√	√	√
• TENS	-	√	-	√	√	√	√	√	√
• SCS	-	√	-	√	√	√	√	√	√
• Nerve blocks	-	-	-	√	√	√	√	√	√
• Placebo	-	-	-	√	√	-	-	-	-
Psychiatric evaluation eg. MMPI	√	√	-	√	√	√	√	√	√
No history of drug addict/abuse	√	-	-	-	-	-	√	√	√
No medicolegal issues	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	√	Unknown
Trial intrathecal given:	√	√	√	√	√	√	√	√	√
• With drugs	-	√	-	√	√	√	√	√	√
• With placebo	-	√	-	-	-	-	-	-	-
• Duration of trials (days)	-	2 - 3	-	-	-	-	½ - 3	Up to 14	2
• No of successful trial	-	11/?	-	90/?	363/429	120/120	30/40	16/25	12/?
Criteria for permanent pump:			Unknown		Unknown				
• % of pain reduction during trial	≥ 50%	≥ 50%	-	Any	-	≥ 60%	≥ 50%	> 50%	≥ 50%
• Side effects during trial	-	Tolerable	-	-	-	-	-	Tolerable	-
• Placebo response	-	No response	-	-	-	-	-	-	-
Additional systemic analgesic/opioid	Unknown	Unknown	Unknown	Yes	Yes	Yes	Yes	Yes	Yes

Table 2. Patient selection criteria for intrathecal morphine or fentanyl for chronic nonmalignant pain. *Continued.*

Reference no.	16	17	21						
Criteria									
Study design	Expert	Expert	Policy						
Number of cases recruited	-	-	-						
Age (years)	-	-	-						
Sex:	-	-	-						
• Male									
• Female									
Patients with failed back surgery	-	-	-						
Intrathecal drugs given*	-	-	e.g. M						
Pump type*	-	-	-						
Pain type:		Clear physiologic origin of pain	Severe chronic intractable pain						
• Nociceptive	√								
• Neuropathic	-								
• Mixed	√								
• Other (visceral, deafferentation)	-								
Previous oral opioid ?	√	√	√						
Previous oral opioid effective ?	Yes	Unknown	-						
Replacement for oral opioid due to SE	√	Unknown	-						
Previous treatments failure, such as:	-	√	√						
• TENS									
• SCS									
• Nerve blocks									
• Placebo									
Psychiatric evaluation eg. MMPI	√	√	-						
No history of drug addict/abuse	√	√	-						
No medicolegal issues	-	√	-						
Trial intrathecal given:	√	√	√						
• With drugs	√								
• With placebo	-								
• Duration of trials (days)	-								
• No of successful trial	-								
Criteria for permanent pump:		-	Adequate relief						
• % of pain reduction during trial	≥ 50		Acceptable						
• Side effects during trial			-						
• Placebo response			-						
Additional systemic analgesic/opioid			-						
Other	Client Expectation	Multidisciplinary	-						

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Other readings of interest:

1. Bennett G, Deer T, Du Pen S et al. Future directions in the management of pain by intraspinal drug delivery. *Journal of Pain and Symptom Management*. August 2000;20(2):S44-S50.

This article provides information on the hierarchical selection of the type of drugs that need to be considered in providing intrathecal treatment for chronic pain. The authors suggested that fentanyl and sufentanil, as third line therapies, were not the priority in future research. Research priority should be given to morphine or hydromorphone. This is an expert opinion article (Evidence Level 4).

2. Bennett G, Burchiel K, Buchser E et al. Clinical guidelines for intraspinal infusion: report of an expert panel. *Journal of Pain and Symptom Management*. August 2000;20(2):S37-S43.

This article provides diagrammatical clinical guidelines for the use of intraspinal drug infusion in pain management. The authors suggested that morphine should be the first line of intrathecal treatment for pain management. Morphine/bupivacaine or morphine/clonidine or hydromorphone (if adequate analgesia with morphine but has intolerable side effects) as the second line of treatments. Fentanyl or sufentanil, morphine/bupivacaine/clonidin is given as the third line of treatment when there is inadequate response toward the second line of treatment. This is an expert opinion article (Evidence Level 4)