Intrathecal Infusion of Opioids

Evidence of effectiveness

2 guideline (2 included)   ~  ~
2 systematic reviews (2 included)   ~/+  ~
1 experimental study (1 included)   ~/~
3 observational studies (1 included)   1.5  0.5  0.5

Evidence of safety and harm

10 other reports
2 reports appraised as low quality

Generic legend:
n/a - not applicable
n/s - not stated
n/r - not relevant
? - unsure or unclear
<table>
<thead>
<tr>
<th>study authors and year</th>
<th>study design</th>
<th>exposure / comparison treatment (number of studies included)</th>
<th>common outcomes among studies</th>
<th>results</th>
<th>validity / applicability</th>
<th>conclusions, comments and quality scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manchikanti, L., Staats, P. S., Singh, V., Schultz, D. M., Vilins, B. D., Jasper, J. F., et al. (2003). Evidence-based practice guidelines for interventional techniques in the management of chronic spinal pain. Pain Physician, 6(1), 3-81.</td>
<td>This is a guideline document – including studies on patients suffering with chronic spinal pain eligible to undergo commonly utilised and effective techniques, various follow up and outcomes.</td>
<td>Intrathecal implantable intrathecal drug administration systems of any type of medication, including baclofen, morphine and clonidine</td>
<td>Moderate evidence of long-term effectiveness, but only basic descriptive information on each study with summary of study outcome provided. No analysis of studies by type of medication. Note: No grading of evidence or systematic, qualitative assessment of included studies. No common outcome analysis performed on included studies.</td>
<td>n/a</td>
<td>Yes</td>
<td>Validity: + Precision: – Applicability: – Overall quality: – Authors’ conclusions: Moderate evidence of long term effectiveness of intrathecal infusion system Reviewer’s comments: Given the lack of grading of evidence, qualitative assessments and common outcome analysis, authors’ conclusion appears overly positive, especially as 2 of the studies referred to have been reviewed here and have been assessed as poor quality.</td>
</tr>
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<td>Sanders, S. H., Harden, R. N., Benson, S. E., &amp; Vicente, P. J. (1999). Clinical practice guidelines for chronic non-malignant pain syndrome patients II: An evidence-based approach. Journal of Back &amp; Musculoskeletal Rehabilitation, 13(2-3), 47-58.</td>
<td>Search Medline, psych-scan, med web 1995-Sept 1999. Included study design: “Well designed” prospective controlled outcome studies. The guidelines are to be applied to chronic pain syndrome patients wherever possible regardless of the site or etiology of persistent pain. This includes Pain disorder associated with Psychological factors, pain disorder associated with both psychological factors and a general medical condition and pain disorder associated with a general medical condition and pain disorder associated with a general medical condition (one not maintained or significantly affected by psychological or behavioural factors). Guidelines not to be applied to cancer, acute, or sub acute pain, or to patients experiencing chronic pain who do not meet chronic non-malignant pain syndrome (CPS) criteria.</td>
<td>Various interventional pain management techniques including: Primary treatment modalities Medication management Physiotherapy and occupational therapy Behavioural/psychological therapy Vocational rehabilitation and disability management Nerve blocks and trigger point injections Acupuncture More invasive procedures (spinal stimulators, continuous infusion devices, brain stimulation)</td>
<td>Recommendations in the guidelines were developed using the scientific evidence. There was no use of any scale for rating the evidence for any of the interventions outlined in this guideline report. One new study identifies (Marion and Loeser, 1996). The authors concluded “inadequate evidence for the application of opioids infusions”. It was not clear which sites were considered in this guideline document. The authors do not recommend opioid infusions.</td>
<td>Focussed question thorough search strategy search terms defined appropriate inclusion / exclusion criteria two reviewers – selection study validity rated two reviewers – validity valid combination of studies appropriate analysis all important outcomes considered balance between benefits and harms fair conclusions from evidence</td>
<td>Validity: +/- Precision: ~ Applicability: + Overall quality: – Authors’ conclusions: Opioid infusions are not recommended for patients with CPS Reviewer’s comments: This guideline document has limited information about the process used to identify, select and evaluate the studies included as evidence. This guideline set is an update of guidelines issued in 1995.</td>
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</table>
**Systematic Reviews**

**study authors and year**

**study design**
Objective: assess the use of intrathecal pump systems for giving opioids in the treatment of chronic pain. Focus is to answer the following questions: which drugs and dosages are commonly used in clinical practice; how effective is this therapy compared with other treatments; what are the risks; what types of patients are suitable; how costly is this type of treatment compared with other treatments; what are the opinions of a group of UK pain specialists about this form of treatment?

**Interventions:** different types of intrathecal pump systems for giving opioids in chronic pain control - different types of intrathecally administered drugs given by pump systems (e.g. opioids, local anaesthetics, clonidine, midazolam, noradrenaline) - comparisons of intrathecal delivery systems with other routes of analgesia delivery (e.g. oral, subcutaneous, rectal, intra-muscular, intravenous, transdermal, intraventricular, neuroaxial, neurolytic and neurosurgical interventions).

**Outcomes:**
- efficacy measures including: visual analogue scale (VAS), verbal rating score, McGill Pain Questionnaire (MPQ), Brief Pain Inventory, range of movement, ability to return to work.
- side-effects: (a) pharmacological side-effects (e.g., respiratory depression, effects on motor and/or autonomic function, nausea and/or vomiting, urinary retention, pruritis); and (b) complications (e.g., local infection, abscess, formation, meningitis, bleeding/haematoma, formation, pump pocket seroma, cerebrospinal fluid (CSF) leaks, dural fistula, improper pocket placement, catheter kinking, catheter obstruction, catheter dislodgement, catheter disconnection, catheter malfunction, pump failure).

**Methods:**
- searched MEDLINE, EMBASE, CancerCD and PubMed. Studies were sought that included the following criteria were used to select studies.
- Population: patients with chronic cancer and non-cancer pain based in a hospital, hospice or community setting (all acute pain was excluded, e.g. labour, postoperative and trauma pain).
- reviewed 114 studies, but no randomised controlled studies or comparator studies were found. Studies included many different interventions (pump types and drugs), many different patient types, and many different outcome measures applied at different times. The data are low grade, falling at the bottom of the hierarchy of evidence.

**Results:**
- of 114 studies, 53 presented data on effectiveness of pump systems. 16 of the 53 reported visual analogue scores before and after pump usage. Average scores declined from 7.6 to 3.3 over a variable period of up to 2 years. All other measures of effectiveness, including various quality of life indicators, invariably reported positive effects.
- Most commonly used intrathecal drug was morphine, followed by morphine in combination with bupivacaine.
- Dose escalation: reported dose increases of between 7% and 100% per week.
- No evidence found to show that intrathecal opioid treatments are superior to existing analgesic treatments such as tablets or injection.

**Authors' conclusions:**
- One study evaluated intrathecal therapies in cancer and non-cancer patients and concluded they were not recommended for non-cancer patients.
- 5 of the 114 studies evaluated use of intrathecal opioids in patients with non-malignant pain specifically (Bloomfield et al., 1995 (n=50); Hasenbichler et al., 1995 (n=18); Nitescu et al., 1998 (n=96); Winkelmuellers and Winkelmuellers, 1996 (n=120); Yoshida et al., 1996 (n=18)). 4 showed generally positive effects. 5th concluded intrathecal therapy was not useful for long-term management of patients with failed back surgery as 'risks and sequelae of pump insertion far outweighed benefits gained'.

**Adverse effects:**
- Pharmacological side-effects attributable to drugs used were reported in 5-26% of patients. Major side effects: nausea/vomiting (25%), sedation (19%), pruritis (17%), myoclonic activity (18%), respiratory depression (3%). Other side effects reported: amnionitis, altered libido, constipation, oedema, polyarthralgia, sweating, incontinence, provocation of asthma, haematoma/seroma/ fistula.
- Other results: meningitis (3%), drug abuse, overdose.
- Mechanical complications associated with the pump delivery systems were reported in up to 25% of patients: catheter dislodgement (5-18%), CSF leakage 10%, other (kinking, obstruction occlusion, migration, pump failure).

**Conclusions:**
- While the data from case series indicate a generally positive effect of intrathecal pump systems, it is difficult to draw definite conclusions because the quality of the data is so poor.
- Overall, the use of intrathecal therapy in patients with chronic pain seems to be beneficial but clearer and more standardised information is required before definite conclusions can be drawn regarding its effectiveness compared with existing treatments.

**Reviewer's comments:**
- Thorough systematic review that includes some material and comment specifically on the use of intrathecal pump systems for non-cancer chronic pain patients (NB: 2 of the 5 studies included in this review are reviewed here [Nitescu et al., 1998 and Winkelmuellers and Winkelmuellers, 1996]).
### Systematic review

**Aim:** to compare the efficacies, failure rates, and technical complication rates of intrathecal treatments (epidural or intrathecal) in patients with refractory non-malignant pain conditions.

**Methods:** a systematic review of clinical studies included: 21 studies (all case series – no randomized controlled studies) reporting on intrathecal administration of opioids with or without a local anaesthetic (bupivacaine) in non-malignant pain – studies included a total of 1,136 patients.

**Results:**

#### Pain relief

- **Intrathecal approach:** compared with the epidural approach, associated with higher rates of satisfactory pain relief for both externalised (86/90, 95% vs. 17/46, 42%, p < .0001) and internalised (295/336, 89% vs. 33/56, 59%, p < .0001).

- **Efficacy and technical complications:**
  - Rates of satisfactory pain relief lower in patients treated with epidural opioids (43/89, 48%) than in those treated with intrathecal opioids (285/323, 88%, p < .0001), intrathecal opioids and bupivacaine (96/183, 93%, p < .0001), and epidural opioids and bupivacaine (77, 100%, p < .05).

- **Technical complications:** highest rates of satisfactory pain relief defined as >40% reduction of initial pain intensity; discontent with treatment; refusal to continue treatment; adverse effects making treatment uncontrollable.

#### Treatment failures

- **Unsatisfactory pain relief defined as:**
  - Treatment failures with the intrathecal approach:
    - Higher rates of treatment failures compared with the epidural approach.
  - Treatment failures with the epidural approach:
    - Higher rates of treatment failures compared with the intrathecal approach.

#### Technical complications

- **Intrathecal approach:**
  - Rates of satisfactory pain relief lower in patients treated with epidural opioids (43/89, 48%) than in those treated with intrathecal opioids (285/323, 88%, p < .0001), intrathecal opioids and bupivacaine (96/183, 93%, p < .0001), and epidural opioids and bupivacaine (77, 100%, p < .05).

- **Efficacy and technical complications:**
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#### Other complications

- **Other complications more frequent with epidural than intrathecal catheters:**
  - Local discomfort along catheter track (8/105, 8% vs 0/101, 0%, p < .01) and epidural/intrathecal fibrosis (21/75, 28% vs 1/101, 1%, p < .0001)

### Conclusions

- **Epidural opioids associated with lower rates of satisfactory pain relief compared to intrathecal opioids or opioids and bupivacaine, and epidural opioids and bupivacaine.**

- **Intrathecal administration of analgesics has advantages over epidural administration:**
  - Requires smaller daily doses
  - More suitable for administration of low volumes
  - Lower rates of technical complications
  - Particularly catheter leakage and obstruction

**Reviewer’s comments:**

- Virtually no detail on the search and selection process used, though good synthesis of pooled study data.
- Study partly funded by grants from families and friends of patients with “refractory” pain treated with intrathecal morphine-bupivacaine in Gothenburg, Sweden.

**Weaknesses of review noted by investigators include:**

- Different types of pain were treated in the different studies (e.g. some studies had patients with a neurogenic component to their pain, which is accepted to be more resistant to intrathecal treatment).
**Infusion: Intrathecal Opioids**


<table>
<thead>
<tr>
<th>Controlled trial (Prospective)</th>
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<tbody>
<tr>
<td>Agents: opioids (morphine; hydromorphone, fentanyl; oxycodone; baclofen; bupivacaine)</td>
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<tr>
<td>Participants</td>
<td>All subjects were receiving treatment for chronic pain at a private pain and headache treatment centre, Derby, USA. N=110</td>
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<tr>
<td>Study design</td>
<td>Inclusions: a) 21-75 years of age; b) no medical or psychological contraindications for IT pain therapy; c) either candidates for IT therapy for pain control or newly registered pain patients who consented to provide questionnaire data. There were 3 different study groups: 1) Group 1-PR: 38 intrathecal pump recipients - selected on basis of results of 3-day inpatient trial of intrathecal morphine patients who experience at least 50% reduction of pain without severe side effects after the trial were offered option of permanent IT pump implant. 2) Group 2-NR: 51 intrathecal candidates who either had an unsuccessful trial, or declined intrathecal (IT) therapy. 3) Group 3-NP: 41 newly referred patients who managed the practice over a 4-month time period.</td>
</tr>
<tr>
<td>Study inclusion/ exclusion</td>
<td></td>
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<tr>
<td>Study authors</td>
<td>Thimineur, M., Kravitz, E., &amp; Vodapally, M. S.</td>
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<tr>
<td>Outcomes</td>
<td>The following data analysed at study entry, and at 6-monthly intervals for a 3-year period: 1) Symptoms Check List 90 (SLC-90), VAS, Pain drawing, McGill (total score). 2) Physical function-SF 36, physical function subscale, OSI. 3) Mood-SCL-90R, depression (DEP) and anxiety (ANX) subscales. BDI. Total daily doses of morphine equivalent calculated for all subjects at baseline and 36-month evaluation. Baseline and 36-month doses of hourly transdermal fentanyl also calculated. Other adjuvant medications not analysed.</td>
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<tr>
<td>Study design</td>
<td>Intrathecal (IT) opioid therapy consisting of: a) implanted intrathecal catheter and constant flow or programmable pump (Medtronic); b) intrathecal drugs and doses adjusted and changed according to symptoms of pain and side effects. (Most patients in Group 1-PR were on more than one IT medication. Most common combinations were: opioid and clonidine; morphine and fentanyl; hydromorphone and fentanyl; small number of patients received other compounds such as baclofen &amp; bupivacaine.); c) pump set-ups performed by trained nurse in the technique of pump.</td>
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<tr>
<td>Participants</td>
<td>Subjects in all groups received either pain therapies as per the standard of care in the practice including oral and transdermal medications, psychological counseling and behavioural treatments, therapeutic injections (trigger point injections, spinal injections, nerve blocks), and physical therapy. Follow-up: 3 years</td>
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<tr>
<td>Participants</td>
<td>Group 1-PR patients showed significant improvement on all pain measures at 36 months. Group 1-PR group also showed improvement at 36 months (for 3 out of 4 measures). Group 2-NR pain scores had significantly worsened by 36 months.</td>
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<tr>
<td>Randomised</td>
<td>Method described: Randomised Intention to treat</td>
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<tr>
<td>Methodology</td>
<td>Blinding appropriate</td>
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<tr>
<td>Generalisability</td>
<td>Yes</td>
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<tr>
<td>Feasible/Affordable</td>
<td>Yes</td>
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<tr>
<td>All important outcomes considered</td>
<td>Yes</td>
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<tr>
<td>Balance between benefits and harms</td>
<td>Yes</td>
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</tbody>
</table>

**Conclusions, comments, and quality scores**

<table>
<thead>
<tr>
<th>Type of comparison</th>
<th>Results</th>
<th>Validity / applicability</th>
<th>Yes no n/a n/s</th>
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<tbody>
<tr>
<td>PR treatment and NR control subjects, completed identical questionnaire packets upon entry (baseline) into the study, and at 6-month intervals for 3 years until termination (36 months) of the study. Newly registered patients (NP) completed the same questionnaires only twice, upon initial evaluation and at 36 months.</td>
<td>IT opioid therapy for non-malignant pain should be considered appropriate only when all other conservative medical management has been exhausted.</td>
<td>No</td>
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<td>PR treatment and NR control subjects, completed identical questionnaire packets upon entry (baseline) into the study, and at 6-month intervals for 3 years until termination (36 months) of the study. Newly registered patients (NP) completed the same questionnaires only twice, upon initial evaluation and at 36 months.</td>
<td>Although Group 1-PRs improved, they were still worse off at 36 months than new referrals were at baseline.”</td>
<td>N/A</td>
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<td>Function comparison</td>
<td>At 36 months Group 3-NP showed significant improvement on these measures (ANX, DEP, BDI). Scores for Group 2-NR were significantly worse.</td>
<td>No</td>
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<td>Mood comparison</td>
<td>At 36 months Group 3-NP and Group 1-PR showed significant improvement on these measures (ANX, DEP, BDI). Scores for Group 2-NR were significantly worse.</td>
<td>No</td>
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<td>Oral morphine</td>
<td>At 36 months, average daily oral morphine dose had significantly decreased for Group 1-PR (P &lt; 0.0000) group and increased for Group 3-NR (P &lt; 0.0000) and Group 3-NP groups (P &lt; 0.005).</td>
<td>No</td>
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<td>Transdermal fentanyl</td>
<td>At 36 months, average hourly transdermal fentanyl dose had significantly decreased in Group 1-PR group, but increased in Group 2-NR.</td>
<td>No</td>
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<td>Injection treatments</td>
<td>Trend towards more injections, especially trigger point injections, being administered to Group 2-NR patients and Group 3-NP patients than Group 1-PR patients.</td>
<td>No</td>
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<td><strong>Adverse effects due to intrathecal treatment:</strong></td>
<td><strong>Pharmacological complications:</strong> pump pocket infections in 2 PR subjects <strong>Side effects of IT therapy requiring cessation of treatment were common:</strong> sedation; nausea; edema; hypogonadism in male patients. However, “(no) patient required, or opted for, discontinuation of treatment for these side effects … The side effects … were reported to be no more bothersome in general than those plaguing the non-recipient control patients using oral and transdermal medications.”</td>
<td>No</td>
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**Experimental Study**

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<th>Study authors and year</th>
<th>Study design</th>
<th>Participants</th>
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### Observational Studies

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<tr>
<th>study authors and year</th>
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<th>study inclusion/exclusion</th>
<th>exposure/comparison</th>
<th>outcomes</th>
<th>results</th>
<th>conclusions, comments, and quality scores</th>
</tr>
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<tr>
<td>Deer, T., Chapple, I., Classen, A., Javery, K., Stoker, V., Tonder, L., et al. (2004). Intrathecal drug Delivery for Treatment of Chronic Low Back Pain: Report from the National Registry for Low Back Pain. Pain Medicine, 5(1), 6-13.</td>
<td>Study conducted using data from the National Outcomes Registry for Low Back Pain, which held prospectively collected data from 166 patients with chronic low back pain trialed for suitability for implantable drug-delivery systems (IDDSs). Patients were recruited (Feb 1999-Feb 2000) only from treatment centres with experience in the implantation of a market-released IDDS (i.e., the SynchroMed Infusion System; Medtronic, Inc.; Minneapolis). A representative of Medtronic was a co-author on the study report.</td>
<td>Patients had chronic low back pain (mechanical, neuropathic, and mixed), with or without leg pain, but with greater back pain than leg pain. Underlying causes included: osteoporosis/compression fractures, spinal stenosis, degenerative disc disease, and osteoarthritis, arachnoiditis, unilateral &amp; bilateral radicular leg pain, failed back syndrome. Patients typically had long histories of pain treatments, including systemic opioids (88.2%), epidural steroids (83.1%), physical therapy (83.1%), and back surgeries (76.3%).</td>
<td>Suitability for IDDS was trialed using continuous epidural infusion (53%), continuous intrathecal infusion (25%), single intrathecal bolus injection (14%), and multiple intrathecal bolus injections (8%). Most patients (81.1%) trialled morphine only. Of the 166 patients trialed for an IDDS (mean age 55.6; 54% females), 154 (93%) had successful trials. 136 (82%) were implanted with IDDS. Patients with neuropathic pain trialed with opioids alone had success rate for trials of 89%, versus 100% success rate for trials for patients with mechanical or mixed pain. Follow-up: 12 months</td>
<td>Standardised forms used at all participating centers to gather registry data. An independent research firm managed the data collection process. Data on the following outcome measures were gathered for baseline and/or at 6- and 12-month follow-ups. Numeric pain ratings: assessments of back pain and leg pain on scales of 0-10</td>
<td>Of 136 patients with implants, data was missing from 21% at 6-month follow-up and from 44% at 12-month follow-up. Results below are for those patients for whom follow-up results were available. <strong>Results for implant group:</strong> Numeric pain ratings: investigators report: pain ratings dropped by 48% for back pain and 32% for leg pain at the 12-month follow-up cf. baseline (P &lt; 0.001). Oswestry Low Back Pain Disability scores Successful outcome in functional ability was defined as Oswestry score reduction of at least one level. 65% reduced their Oswestry scores by at least one level at 12-month follow-ups compared to baseline. Satisfaction with the therapy 80% satisfied with their therapy; 87% said would undergo procedure again. 90% said they would recommend the therapy to a family member or friend. <strong>Reviewer’s comments:</strong> Generalisability of the study results limited due to missing data at follow-up visits. No analysis of features of drop-outs cf. retained patients. Patients may have dropped out because they were dissatisfied with the treatment procedures or outcomes.</td>
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### Case series (Prospective)

**Agents:** morphine; various

**Case series score:** 1.5/3

**Authors’ conclusions:** IDDSs are successful in managing chronic low back pain in patients who have not found effective relief with other therapies

Patients with neuropathic pain had a statistically significantly lower success rate.

In patients with neuropathic or mixed pain, use of combined drug therapy may improve the chances of trialling success and long-term outcomes.

**Reviewer’s comments:**

Generalisability of the study results limited due to missing data at follow-up visits. No analysis of features of drop-outs cf. retained patients. Patients may have dropped out because they were dissatisfied with the treatment procedures or outcomes.
### Other Reports (safety and harm)

<table>
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<th>study authors, year, study design</th>
<th>reviewer summary</th>
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<tr>
<td>Coffey, R. J., &amp; Burchiel, K. (2002). Inflammatory mass lesions associated with intrathecal drug infusion catheters: report and observations on 41 patients. Neurosurgery., 50(1), 78-86; discussion 86-77.</td>
<td><strong>Objective of study:</strong> identify number of patients reported to have inflammatory mass lesions of non-infectious origin at tip of intraspinal drug administration catheters; evaluate hypotheses for cause of lesions. <strong>Data sources:</strong> published medical literature and unpublished case data reported by Medtronic, Inc (a manufacturer of catheters) to the United States Food and Drug Administration (up to Nov, 2000). <strong>Results:</strong> 41 cases identified, with just 16 identified from the published literature. All 41 patients were being treated for chronic pain. Mean duration of intrathecal drug infusion therapy = 24.5 months (range 0.5-72 months). 36/41 = non-cancer related pain, including 24 with pain from failed spinal surgery. <strong>Level of catheter tip and lesion:</strong> Thoracic 28/41 Lumbar 5/41 Not reported 8/41 <strong>Intrathecal drugs:</strong> 39/41 cases = morphine or hydromorphone, either alone or mixed with other drugs. Morphine dosage was ≥ to 15 mg/d in 7 patients, and morphine concentration was ≥ 25 mg/ml in 15 patients. “No masses were reported in patients who received baclofen as the only intrathecal medication.” <strong>Clinical outcome:</strong> 30/41 had surgery to relieve spinal cord or cauda equina compression. 11/41 were non-ambulatory at last follow-up</td>
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<p>| Authors’ conclusions: Possible cause of non-infectious lesions at catheter tip. Authors hypothesise that “CSF flow dynamics within the spinal canal, in combination with the physical, chemical, and/or immunological properties of approved intrathecal opiates and some unapproved drugs, may be responsible for the growth of inflammatory mass lesions at the tip of intrathecal drug delivery catheters. Previous spinal surgery or normal variations in the anatomy of the arachnoid membranes may influence the local concentration of intraspinal drugs in an unpredictable way. Positioning the drug administration catheter tip below the conus medullaris may not eliminate the patient's risk of developing a mass, but it does preclude injury to the spinal cord.” |</p>
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<th>study authors, year, study design</th>
<th>reviewer summary</th>
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**Authors begin by noting finding from other studies which show:**

1) continuous intrathecal infusions of morphine, bupivacaine, and baclofen are used to manage a variety of chronic medical problems.

2) reported complications have been rare and include:
- catheter failure
- dose-associated effects of opiates
- local infections temporally associated with pump insertion
- epidural abscesses
- meningitis

Authors add there are “several reports of granulomatous lesions developing near the catheter tip in patients receiving long-term infusion of morphine by means of implanted pumps”. However, “none of the lesions were described as an abscess and all appeared to have occurred on the same side of the dura as the catheter tip. The cause of these granulomas has not been established, although it has been suggested that they may be a local inflammatory reaction to morphine.”

**Outcome:**

The cluster of severe neurologic complications was determined to be the result of medical errors in an outpatient pharmacy. Errors in the pharmacy led to inadvertent administration of methadone, and perhaps other substances (ethanol), by means of implanted intrathecal catheters.

| Background to incident: | Total of 61 patients in one neurosurgical practice received pain medication through implanted intrathecal catheter pumps, including 19/61 treated with morphine, either alone or in combination with other medications. None of the 42 patients whose drug regimen excluded morphine developed a complication. However, 8 of 13 patients provided with morphine in refills of their pumps during one 4-week period experienced neurologic complications.

Lesions observed in the affected patients were heterogeneous and included an epidural abscess, an abscess that was both intradural and extradural, and an abscess within the conus. All the abscesses were sterile. Three patients underwent laminectomy for sterile abscesses and were left with new paralysis or leg weakness.

“Testing of two stock bottles from the involved pharmacy, both labelled as containing pure morphine, revealed the presence of methadone in addition to morphine. One of these bottles also contained trace ethanol. A sample of medication aspirated from the pump of a patient prescribed morphine from the same pharmacy was also found to have contained methadone and methanol.” Incident involved two drugs with similar names and packaging. Errors stemming from confusion may have occurred. |
objective of study: investigate hypothesis that intrathecal opioids suppress hypothalamic-pituitary-gonadal axis

authors report other studies show: intrathecal opioids associated with amenorrhea in females, impotence in males, and loss of libido in both sexes.

cross-sectional studies indicate low testosterone levels in men treated with intraspinal opioids, also suppression of gonadotrophins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH] in postmenopausal women) - consistent with central suppression of the hypothalamic-pituitary-gonadal [HPG] axis.

some studies suggest symptoms of sexual dysfunction recover in time despite ongoing intrathecal opioid administration, but cross-sectional studies do not support this conclusion.

characteristics of patients:

10 males with chronic noncancer pain: mean age 52 ± 4 (range 25-64); diagnoses = lumbar spinal pain after failed spinal surgery (n = 4), complex regional pain syndrome type 1 (n = 3), cervical discogenic pain (n = 1), post-thoracotomy pain syndrome (n = 1), central pain (n = 1). average pain duration = 11.5 years (range 0.8-24). 4/10 patients taking antidepressants.

exclusions: testosterone supplementation in previous 3 months.

outcomes measured at baseline and during first 12 wks of intrathecal opioid infusion therapy:

- doses of both opioid and nonopioid medication.
- symptoms of HPG axis function:
  - libido (graded as good, average, or poor)
  - frequency of sexual intercourse
  - frequency of masturbation
  - difficulty obtaining an erection
  - ability to obtain an erection sufficient for penetration
  - presence of early morning erections
  - reduction in body hair
  - breast enlargement
  - nipple discharge.
- physical examination
  - assessment of testicular volume using Prader orchidometer
  - measurement of testicular length
  - grading of body hair distribution according to the stages of Tanner
  - breast examination for gynaecomastia and galactorrhea.
- hormonal assays
  - serum testosterone, LH, FSH, prolactin, and sex hormone-binding globulin.

results:

“Mean intrathecal opioid doses were 2.6 ± 0.5, 3.3 ± 0.6, and 5.3 ± 1.2 mg morphine equivalents at 1, 4, and 12 weeks, respectively.”

intrathecal opioid administration resulted in significant (p < 0.0001) reduction in serum testosterone:

- baseline 7.7 ± 1.1 (mean ± SEM) nmol/L
- 1 week 2.0 ± 0.7 nmol/L
- 4 weeks 2.8 ± 0.5 nmol/L
- 12 weeks 4.0 ± 0.9 nmol/L

throughout the study, all other hormone levels remained close to their reference range, although there was a significant (p < 0.0001) decrease in FSH levels.

“Luteinizing hormone and follicle-stimulating hormone levels remained within reference ranges, indicating central rather than peripheral suppression.”

above changes associated with reduction in libido and potency. at baseline, “most” subjects had poor libido and abnormal erectile function. but an increasing number reported sexual dysfunction during the 12-week study period. at 12 weeks, no subjects sexually active. “poor libido was almost universal.” (authors note sexual dysfunction is common in patients with chronic pain – may relate to several factors including psychological factors especially depression, passive coping strategies, catastrophising, control appraisal, fatigue, medication, neurologic injury from disease or previous surgery).

authors’ conclusions:

intrathecal opioid therapy in men results in suppression of the HPG axis and a decline in serum testosterone levels.

long-term administration of low-dose opioids via the intrathecal route may improve quality of life by providing improved pain control, but effect on sexual function may compromise this quality.

hypogonadism is a risk factor for spinal osteoporosis in men - associated with an increased risk of vertebra and hip fractures.
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<th>Study Authors, Year, Study Design</th>
<th>Reviewer Summary</th>
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**Patient Group:**  
n=108 patients (56 cancer patients, 52 non-cancer patients) treated with intrathecal bupivacaine (average dose: 10 mg/d, range: 2-25 mg/d) and opioids for an average duration of 86 weeks.  

**Inclusions:** failure of more conservative treatments to provide pain relief; life expectancy of at least 3 months for cancer patients; absence of untreated psychiatric disorder in non-cancer patients; has appreciable pain relief and acceptable side effects following screening with continuous neuraxial opioid infusion (either morphine or hydromorphone);  

**Intrathecal Infusion Treatment:**  
Patients had received intrathecal bupivacaine for an average of 86 weeks (range: 10-301 weeks)  
Bupivacaine was administered to 108/108 patients at an average dose of 10 mg/d (range: 2-25 mg/d).  
Morphine was administered to 101/108 patients at an average dose of 8 mg/d (range: 1-22.5 mg/d).  
Hydromorphone was administered to 7/108 patients at an average dose of 1.5 mg/d (range: 0.1-3.8 mg/d).  

**Clinical Assessments** of patients made approximately every 4 weeks and comprised:  
1) collection of patient histories regarding side effects, systemic problems, and degree of pain relief as well  
2) neurologic examination  
Twenty-nine percent of the patients also underwent a repeat imaging study (magnetic resonance imaging), and 12 patients had an electromyogram and nerve conduction study in the follow-up period. |

**Safety and Harm**  
Agent: bupivacaine  
NB: The investigator was affiliated to Medtronic Inc, a major manufacturer of infusion delivery systems. | **Results:**  
Investigators report finding no clinical evidence of drug-induced toxicity or complications in any patient when bupivacaine doses of between 2 and 25 mg/d were combined with intrathecal morphine or hydromorphone.  

“None of the 108 patients followed for a combined total of 14,384 weeks displayed any evidence of bupivacaine-induced side effects, toxicity, or neurologic changes that could not be attributed to the progression of their primary disease.”  

Investigators note that potential dose-dependent side effects previously ascribed to intrathecal bupivacaine infusion include:  
- paresthesia  
- paresis  
- gait impairment  
- urinary retention  
- orthostatic hypotension.  

**Authors’ Conclusions:**  
Chronic supplementation of intrathecal opioids with bupivacaine is a safe method for providing continued management of chronic pain of cancer or noncancer origin.  

Supplementing opioid therapy with bupivacaine allows patients to continue to be effectively managed using an implantable intrathecal delivery system. |

**Safety and harm**

Agents: morphine; baclofen

N.B. study results not separated for malignant and non-malignant pain patients.

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<th>study authors, year, study design</th>
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<th>Reviewer’s comments:</th>
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A multicenter, prospective study measuring complications during the long-term use of a one-piece intrathecal catheter system for delivering drugs (morphine or baclofen) to treat non-malignant and malignant pain, and spasticity.

The type of one-piece catheter system was Model 8709, manufactured by Medtronic Inc, Minneapolis, USA.

Inclusions: age 18 or older, diagnosis of intractable pain of malignant or non-malignant origin or spasticity of spinal cord origin; candidates for intrathecal administration of morphine or baclofen.

A total of 209 patients were studied at 22 participating centers, with 1764 cumulative patient-months of catheter experience. 72.7% of the patients had pain of non-malignant origin (diagnoses not specified); 22.5% had cancer pain; 4.8% were undergoing treatment for spasticity.

Data related to the safety and performance of the catheter system were collected at implant, and at 1, 3, 6, and 9 months post-implant. Data were also gathered at each pump refill, and whenever catheter complications occurred.

A catheter-related complication was defined as: “any adverse event that was considered to be associated potentially with the catheter system, but not necessarily caused by it.”

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<th>Number of complications</th>
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<td>49 catheter system complications occurred in 37 patients (N.B. results not separated for malignant and non-malignant pain patients):</td>
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<td>- 7/49 complications related to the catheter itself</td>
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<td>- 42/49 complications related to the catheter implantation procedure.</td>
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**Other relevant background material:**
The investigators’ review of the literature indicates that common catheter-related complications include: kinking, dislodgments, disconnections, breaks or tears, and occlusions of the catheter. “Catheter complications requiring surgical correction range in incidence from 10% to 89%, but are reported in most clinical series as occurring in approximately 20-25% of implanted systems.”

However, because information on safety and harm was included in the study abstract, a summary of the safety and harm information reported by the investigators is provided here.
**Objective of the study:** to report on the details of a single case of spinal cord compression syndrome associated with the use of an intrathecal pain management pump system.

**Author notes findings from other studies showing:** problems with fibrosis at the tips of intrathecal catheters, including fibrosis resulting in spinal cord compression. These studies suggest the symptoms of cord compression “may become evident sooner when the catheter is placed at the cervical or thoracic level because of the limited space in the spinal canal at those levels”.

Studies also describe the most common signs and symptoms indicating probable malfunction at the site of the catheter tip; 1) breakthrough pain on a regimen that had previously controlled symptoms; 2) pain symptoms only temporarily relieved by increasing the dose of intrathecal medication, whereas previously small increases in dose had adequately controlled the pain. Another sign is “puffiness” along the catheter.

**Patient:** 45-year-old woman with history of chronic low back pain; intrathecal infusion pump (Medtronics Infusaid) permanently placed for pain and spasm control 26 months earlier. Reservoir for pump was implanted in anterior abdominal wall; catheter tunnelled around left lateral abdominal wall at the level of L-2 and secured with the tip of the catheter at T-12/L-1 level in intrathecal space of spine.

**Presenting symptoms:** patient described that in the previous 8-10 months there had been a marked decrease in both her pain relief and spasm control, despite increases in her daily dose of intrathecal morphine and addition of bupivacaine. In month prior to presentation she reported:
- increased numbness in buttocks, thighs and feet
- increasing difficulty walking, could not feel where her feet were and that her legs were weak.
- recent onset of difficulty holding urine and moving bowels.

Bupivacaine dose had been gradually reduced to zero but symptoms persisted.

**Investigations and findings:**

*Physical examination:* otherwise healthy woman; normal vital signs; anterior abdominal subcutaneous ‘pump’ appeared to be neither swollen, red nor warm; laminectomy scar noted over lower lumbar spine; small puffy, slightly tender, but not red nor warm area noted subcutaneously under the spinus process of L-2; bilateral lumbar paraspinal muscle spasm and tenderness; spasm and tenderness muscles of bilateral lower extremities.

*Neurological evaluation:* decreased sensation to pin prick and two point discrimination over buttocks, perineum and inner and anterior thighs to the level of the knees and over the soles and medial aspect of both feet; zero position sense in left great toe; diminished position sense in right great toe; assessment of walking abilities revealed hesitant, searching movements of both legs before placing each step, difficulty transferring weight from leg to leg because of ‘wobbling' movements of both legs; strength of all lower extremity muscles were within normal limits but plantar and patellar reflexes near absent to absent.

*Magnetic resonance imaging* (MRI – with and without contrast) of thoracic and lumbar spine indicated a mass at the site of the tip of the intrathecal catheter; lesion was producing a high grade spinal cord compression at the level of L-1.

*Surgical exploration:* laminectomy identified a reactive tissue fibroma tenaciously adherent to the spinal cord and catheter all the way back to the previously identified subcutaneous ‘puffy lump’ at the level of L-2. This was removed.

*Histology* indicated fibroma to be a ‘well defined soft tissue mass showing central acellular necrosis surrounded by a rim of granulation tissue with a focally dense infiltrate of mixed inflammatory cells, predominantly lymphocytes and plasma cells and an early ingrowth of fibrocollagen’.

**Authors’ conclusions:**

With the increased use of intrathecal permanent infusion pump delivery systems for patients with chronic pain and spasm conditions, health professionals must be alert to the possibility of cord compression syndrome in patients presenting with symptoms of increasing low back pain, anaesthesia and progressive proprioceptive loss. This is important for preventing potentially catastrophic irreversible neurologic complications.
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<th>study authors, year, study design</th>
<th>reviewer summary</th>
<th>Drug toxicity</th>
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<td>Du Pen, S. L. (1998). Implantable spinal catheter and drug delivery systems: Complications. Techniques in Regional Anesthesia &amp; Pain Management, 2(3), 152-160.</td>
<td>This study reviews the literature on complications associated with the use of implantable epidural and intrathecal drug delivery systems. The investigators note that the potential complications associated with spinal drug delivery systems, along with cost, are the biggest barriers to the widespread use of these techniques. The investigators state that subcutaneously implanted pump systems are primarily used for intrathecal infusion delivery (the advantages and disadvantages of these systems are compared with epidural catheters designed for short-term use, permanent epidural catheters designed for long-term use, and implanted epidural ports where the catheter/port is completely internal). The investigators observe that epidural delivery systems have been widely used in the advanced cancer patient population, but that “generally, cost and infection risk has driven most US practitioners to use only totally internalized systems for non-cancer patients”. The review indicates, based on studies of cancer-pain patients as well as studies of non-cancer pain patients, that complications associated with long-term spinal drug delivery systems fall into three main groups: infection, drug toxicity, and mechanical problems. The description of these complications given by the authors focuses mainly on epidural delivery systems (see the Epidural Infusion evidence summary) but some information is given related to intrathecal delivery systems:</td>
<td>- infusion of agents into the epidural or intrathecal space may be associated with drug-related complications, including drug toxicity or drug-related side-effects. -opioid side-effects = nausea/vomiting, urinary retention, constipation, and sedation. -respiratory depression is rare in opioid-tolerant patients. Myoclonic activity is seen less frequently, but can be severe when it occurs. -chronic opioid infusions appear to cause suppression of hormone production, leading to loss of libido. -local anaesthetic side effects include postural hypotension, skin anaesthesia, and motor loss. - abrupt discontinuation of spinal clonidine has the potential to cause rebound hypertension.</td>
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<tr>
<td>Safety and harm</td>
<td>N.B. this review was based on studies of cancer and as well as non-cancer pain.</td>
<td>Mechanical problems</td>
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<td>- the review notes that mechanical problems may be associated with the catheter, pump, filter or the implanted device.</td>
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**Infection**

The investigators state:

- there are rare descriptions in the literature of infection with implanted intrathecal systems

- “the use of externalised intrathecal catheters for chronic drug administration has been considered by most U.S. clinicians as a technique with too many risks”
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Patients: 40 men, 50 women; age 20 to 96 (median, 70 years); group had heterogeneous "refractory" pain conditions; duration of pain 0.3 to 50 years (median, 3 years); other methods failed to provide acceptable pain relief.

Intervention: 1) insertion of externalized, tunneled intrathecal catheters, 2) intrathecal infusion of opioid (morphine 0.5 mg/ml, or buprenorphine 0.015 mg/ml, and/or bupivacaine 4.75-5.0 mg/ml) from external electronic pumps at basic rate of 0.2 ml/hour; optional bolus does (0.1 ml 1-4 times/hour). 3) on subsequent days the infused volumes adjusted to give each patient satisfactory to excellent (60-100%) pain relief (with acceptable side effects), by increasing or decreasing basic rates and/or bolus doses, and their timing.

Throughout the intrathecal treatment period, patients also had unrestricted access to nonopioid analgesics/sedatives and opioids administered by various routes (oral, enteral, and/or parenteral) until they obtained acceptable pain and anxiety relief.

**Side effects and complications mainly attributed to intrathecal opioid**
- Symptoms from opioid withdrawal (n = 17)
- Clonus (n = 3)
- Transient confusion/hallucinations (n = 3)
- Constipation (n = 2)
- Nausea and/or emesis (n = 18)
- Pruritus (n = 1)
- Bradypnea (n = 1)

**Side effects and complications mainly attributed to intrathecal bupivacaine**
- (of the patients, who did not have these conditions before the start of the intrathecal pain treatment)
- Transient paresthesiae (35%)
- Transient paresis (22%)
- Episodic arterial hypotension (10%)
- Transient urinary retention (47%)
- Transient urine incontinence (3%)
- Transient fecal incontinence (3%)

Side effects occurred at daily doses of intrathecal bupivacaine ranging from a low of 15 to a high of 130 mg/day (median, 42).

**Other complications**
- Investigators note that details of complications related to:
  - catheterisation technique
  - puncture of the dura mater
  - manipulation of infused solutions and equipment,
  - long-term catheterisation of the subarachnoid space
  are presented in a separate paper (see Dahm et al 1998)

They add that:
- meningitis occurred in 4 of the 90 patients
- 5 patients tried to commit suicide, 3 of them successfully (the 5 patients were described as being affected by severe depression, family conflicts, loneliness, and the meaningless of their life).
- 23 patients died during the treatment. However, none of these deaths were attributed to the long-term intrathecal catheterisation or to the intrathecal administration of opioid-bupivacaine solutions.
- no neurologic sequelae occurred during intrathecal treatment.

**Reviewer's comments:**
Although a case series of 90 patients, the results of the study related to pain are excluded from consideration in this review as 32/90 were reported to have pain related to peripheral vascular damage (arterial insufficiency in the lower extremities with skin ulcerations and / or gangrene); 2/90 were reported to have post-herpetic neuralgia; 5/90 with visceral pain; 2/50 angina

However, because information on safety and harm was included in the study abstract, a summary of the safety and harm information reported by the investigators is provided here.
### Case study (2 patients)

#### Safety and harm

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<th>Study authors, year, study design</th>
<th>Reviewer summary</th>
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<tr>
<td>Becker, W. J., Ablett, D. P., Harris, C. J., &amp; Dold, O. N. (1995). Long term treatment of intractable reflex sympathetic dystrophy with intrathecal morphine. Canadian Journal of Neurological Sciences, 22(153-159).</td>
<td><strong>Objective of study:</strong> report on outcomes of use of intrathecal morphine therapy for treatment of two patients with reflex sympathetic dystrophy. Patients had Infusaid Model 400 infusion pump implanted with an intrathecal catheter. <strong>Reports of intrathecal catheter leak in one of the two patients:</strong> Patient 1: Patient found that she could not shower as the water was painful on her leg; leg became tender to touch, and swollen. She noticed a red rash over the infusion pump site, and this increased in severity. Also leg did not improve with increased concentrations of morphine. She developed headache and nausea. X-ray contrast injections into the pump side port showed a leak in the catheter in the area of her back. Pump catheter was repaired surgically, during which several small holes in the catheter were found. At discharge the rash over her pump site was greatly improved, but the leg did not improve. A further contrast injection into the pump side port showed continued leakage. Entire catheter system replaced surgically. Some months later a rash was noted over patient’s pump site. She developed a headache compatible with a low pressure headache. Rash was felt again to be due to morphine extravasation into subcutaneous tissues from a catheter leak. Contrast injections were done into pump side port, but x-rays could not demonstrate a leak. Leak also could not be demonstrated with technetium radioisotope injections, gamma camera and Spect imaging. Subsequently the patient's catheter system was surgically explored, but a leak could not be demonstrated. However, after the surgery the patient’s headache and nausea rapidly resolved, and the rash over the pump site faded. <strong>Patient 2:</strong> Patient 2 was a child and therefore this case not relevant to this review.</td>
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<td>Authors' conclusions:</td>
<td>1) side effects from this therapy were relatively minimal, with no pump, catheter, or central nervous system infections. 2) Intrathecal morphine dosage: at high doses of intrathecal morphine (up to 108mg per day), both patients noted tolerable but significant side effects of nausea and feeling generally unwell. These side effects disappeared as the dosage was reduced. 3) “Catheter breakage can result in a rapid recurrence of the RSD in these patients, necessitating surgical catheter repair.” “… a red rash appearing over the pump site may the first indication that a catheter breakage has occurred. This rash presumably occurs as a result of histamine release in the skin by the extravasated morphine, and is an indication that the treatment team must evaluate the integrity of the catheter as quickly as possible, and repair it before an exacerbation of the RSD occurs. Under these circumstances, the surgery associated with catheter exploration and repair does not necessarily result in an exacerbation of the RSD if done quickly while the RSD is still under control.”</td>
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Infusion: Intrathecal Opioids

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<th>Study authors, year, study design</th>
<th>Reviewer summary</th>
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<td>Bloomfield, S., Hogg, J., Ortiz, O., &amp; Gross, R. (1995). Analysis of breakthrough pain in 50 patients treated with intrathecal morphine infusion therapy. Development of tolerance or infusion system malfunction. Stereotactic &amp; Functional Neurosurgery, 65(1-4), 142-146.</td>
<td><strong>Subjects:</strong> 50 patients with intractable benign pain treated between 1989 and 1995; 31 males and 19 females; pain etiology included reflex sympathetic dystrophy (12), low back and leg pain [with (9) and without arachnoiditis (8)], painful spasticity (multiple sclerosis 6, spinal cord injury 4), thoracic postherpetic neuralgia (4), abdominal pain (3), phantom limb pain (3), painful dystonia (1); all other standard treatments had been attempted but failed to provide lasting benefit; psychological assessment ruled out secondary gain, conversion hysteria, significant depression. <strong>Treatment:</strong> Intrathecal morphine (IT MS) infusion therapy; 11 patients used an Infusaid IT-MS system, 39 used a Synchromed infusion system (Medtronic). Patients were implanted if they experienced adequate pain relief and had no significant side effects after a trial bolus injection of IT MS. <strong>Follow-up:</strong> median 39 months (range 5-70): <strong>Results:</strong> Breakthrough pain was reported in 45 (90%) patients in 75 outpatient clinic events. A diagnostic algorithm was developed to evaluate these patients and determine treatment options. <strong>Algorithm:</strong> Step 1: Programmed bolus of 50% of patient’s current daily morphine dose was given to all patients with breakthrough pain. If patient benefited from the bolus, they were considered to have become partly tolerant to the IT MS. Their daily morphine dose was therefore increased by 25%. Step 2: If the patient did not benefit from the bolus, a radiographic catheter series was performed to identify catheter malfunction (radiograph perpendicular to the pump; anteroposterior and lateral lumbar radiograph to rule out catheter tip migration, obvious kinking, disconnection, and catheter breakage). If a catheter problem was identified, surgical revision was undertaken. In the 7 events where CSF withdrawal was good, patients underwent surgical revision. Step 3: If the radiographic series was normal, the patient’s side-port was entered with a Tuohy needle to withdraw cerebrospinal fluid (CSF) from the catheter. If CSF was not easily withdrawn from the side-port, then assumed catheter was obstructed and patient underwent surgical revision. If CSF was easily withdrawn then catheter assumed to be functioning well. Step 4: If catheter assumed to be functioning well, patient had myelogram with dye injected through side-port to evaluate flow of dye through the catheter, check for leaks and check flow of dye through the lumbar thecal sac. If scarring found blocking the flow of medication from catheter tip to spinal cord then patient had surgery to either revise the catheter or remove the scarring. Findings using diagnostic algorithm: In 50 of the 75 breakthrough events (67%), patients responded to the programmed bolus and regained pain relief with an increased baseline dose of morphine. In 10 of these 50 events (20%), benefits were maintained with baseline doses below 10 mg of IT-MS/day. Partial tolerance was seen in 23/50 events where baseline doses were increased to 10-35 mg IT-MS daily. Side effects of urinary retention or malaise were seen in 12/50 events after baseline doses were raised beyond 1.5 mg/day to attempt to control breakthrough pain. Once the baseline doses were reduced back to under 1.5 mg/day, these patients gained only minor pain relief. Patients in 5/50 of the events developed true tolerance and lost all initial pain relief benefits despite being given boluses and escalating doses up to 50 mg/day or in 25/75 breakthrough events (33%), patients failed to benefit from the bolus injection and so had the radiographic catheter survey. Catheter malfunction was noted on radiographs in 11 of these 25 events (migration out of the spine 5, disconnection 2, obvious kinking 2, breakage at the level of the ligamentum flavum 1 and breakage at the spinous processes 1). Attempts to withdraw CSF from the side-port in the remaining 14/25 identified catheter obstruction in 7 breakthrough events (surgery identified a kink in 5 and obstruction of the inner lumen in 2). CSF withdrawal was good for the other 7 events. In the 7 events where CSF withdrawal was good, patients underwent side-port myelography. In 1 case scar tissue was found blocking the flow of medication from catheter tip to spinal cord then patient had surgery to either revise the catheter or remove the scarring. The remaining 5 breakthrough events (involving 5 patients) were considered to be cases of true tolerance to morphine. <strong>Investigators’ conclusions:</strong> Breakthrough pain resulting from tolerance development with intrathecal morphine infusion therapy is rare. Breakthrough pain is more commonly caused by either: 1) a malfunction of the infusion system that can be surgically corrected or 2) partial tolerance requiring escalating doses. <strong>Reviewer’s comments:</strong> Four of the 50 patients in this study had thoracic post-herpetic neuralgia, technically disqualifying this case series study from inclusion. However, safety and harm information was included in the study abstract.</td>
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Studies appraised as low quality

Infusion: Intrathecal Opioids

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<tr>
<th>study authors and year</th>
<th>participants</th>
<th>study inclusion/ exclusion</th>
<th>exposure/ comparison</th>
<th>outcomes</th>
<th>results</th>
<th>conclusions, comments, and quality scores</th>
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<tr>
<td>Roberts, L. J. et al. (2001)</td>
<td>Patients: n=88 (58 women, 30 men; mean age 53.4) with chronic non-cancer pain (mean duration 9.8 years) treated at two Perth pain management centres</td>
<td>Treatment with intrathecal opioids administered via totally implanted drug administration systems. 77/88 patients (93%) initially treated with morphine. “Many patients subsequently underwent trials of other agents. These included opioids such as hydromorphone and sufentanil and non-opioids such as bupivacaine and clonidine.” No further details given.</td>
<td>Self-administered questionnaire posted to all patients; those who failed to respond were sent a further questionnaire or surveyed at clinic attendance for pump refill. Global pain relief: (data available only for 49/84 live patients) mean pain relief 60% at time of follow-up. Physical activity levels: (data available only for 49/84 live patients) 74% of patients (36/49) reporting increased activity levels. Medication intake: (data available only for 48/84 live patients) oral med intake was significantly reduced (Medication Quantification Scale Score prior to implantation 31.0 ± 2.6 and at follow-up 12.7 ± 1.4; n = 48; p = 0.0001). Mean intrathecal morphine dose increased from 9.95 ± 1.49 mg/day (mean ± SEM) at 6 months to 15.26 ± 2.52 mg/day 36 months after start of therapy. Work status (data available for 50/54 [90%] patients of working age) No change in work status: 43/50 not working at follow-up. Patient satisfaction: (only 51/84 provided data on patient satisfaction); 19/51 (37%) moderately satisfied; 24/51 (47%) very satisfied. Adverse effects: data available only for 52/67 [78%] patients who returned questionnaires: excessive sweating (62%); weight gain (52%); difficulty with concentrating, thinking, memory (40%); nausea &amp; vomiting (42%); asthenia (25%); peripheral oedema (23%); pruritus (21%); sexual dysfunction (decreased libido 12/17 men, 15/31 women; erectile difficulty 10/17 men); menstrual disturbance (7/15 women under 50).</td>
<td>Case series score: 0.5/3 Authors’ conclusions: “Intrathecal opioid therapy appears to have a role in the management of chronic non-cancer pain.” “Dose escalation did not appear to be a problem in the majority of our patients, however, a number required change to an alternative opioid or the addition of intrathecal adjunctive agents.” “No studies to date have demonstrated a significant change in work status as a result of intrathecal opioid therapy…” Indeed, successful return to work may not be a realistic outcome in this group of patients with very severe non-cancer pain and high levels of disability and dysfunction.” “Further prospective evaluation is needed to determine the precise role and effectiveness of intrathecal opioid therapy within the context of a multidisciplinary assessment and management paradigm, in particular when compared with other less invasive therapies. Intrathecal opioid suppression of the HPG axis requires further assessment” Reviewer’s comments: There was a low response rate to some (important) questions. A retrospective study, with high reliance on patient self-report and recall.</td>
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### Infusion: Intrathecal Opioids

**Study Design**

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<th>Case Series (Retrospective)</th>
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<tr>
<td><strong>Agents:</strong> morphine; also for some patients combined with 1 or more of: buprenorphine, clonidine, fentanyl, bupivacaine, NaCl</td>
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| **Inclusion Criteria:** inability to successfully treat underlying cause of pain; 2) somatically caused pain; 3) unsatisfactory response to peripheral or central analgesic drugs or intolerable side effects; 4) failure of other pain therapy measures (TENS, epidural spinal cord stimulation); 5) exclusion of psychiatric illnesses; 6) patients with or without severe incapacitation; 7) reproductible analgesia through continuous intrathecal test application of opioid agents via an external pump. Of the 120 patients, 82 still receiving intrathecal opioid therapy with a functioning implant when traced for follow-up. (Of remaining 38 patients, implant removed for various reasons in 25/38; 7/38 deceased; 6/38 other reasons.) 49/82 had mixed nociceptive-neuropathic pain due to multiple lamnbo-sacral operations, including spondylodiscitis; 18/82 had stump and phantom pain, complete paraplegia, thalamic pain, peripheral nerve injury, and brachial, as well as lumbar, root avulsions; 10/82 had nociceptive pain following multiple operations on bone and soft tissue or due to meningeal headache. | **Exposure/Comparison**
| Continuous intrathecal opioid therapy via implantable infusion pump systems (in most cases gas driven: pump systems from USA or Germany). Mean morphine dosage initially administered was 2.7 mg/day (range 0.3-12 mg/day) after an average of 3.4 years, it was 4.7 mg/day (range 0.3-12 mg/day). For majority of cases, most effective and best tolerated substance was morphine. In some cases morphine was replaced with buprenorphine because of side effects or development of tolerance. In individual cases, effectiveness of intrathecal treatment increased by addition of clonidine, bupivacaine, or change from morphine to fentanyl. Follow-up: range 6 months – 5.7 years. |
| **Outcomes**
| Data collected at baseline and follow-up using investigators’ own standardised questionnaire: - Pain intensity, self-recorded by patient using Visual Analogue Scale (VAS – range 0 no pain to 100 unbearable pain) using pain diary 3 times/day - Activity level - Mood - Subjective assessment of quality of life |
| **Results**
| Pain Intensity: Mean value assigned to pain intensity prior to pump implantation was 93.6. Six months after spinal opioid infusion therapy began, the mean pain intensity value was 30.3; at end of the last follow-up period, the value was 39.2. Level of Activity: Prior to treatment, 94% reported themselves to be passive or withdrawn socially due to intense pain compared to 43% at follow-up (p < 0.001). Mood: Prior to treatment, 88% of patients described themselves as “despairing and depressed.” At end of follow-up, 67% indicated they were either satisfied with their condition or only “slightly bothered” by the pain (significant difference before and after treatment p < 0.001). Quality of life: At end of follow-up, 81% of patients reported the current therapy had improved their quality of life, 92% satisfied with the therapy and 90% satisfied with the follow-up treatment. Side effects: Sweating (8.5%) and oedema formation (6.1%) were the most common lasting side effects of morphine therapy. Side effects reported at the beginning of treatment included constipation, disturbed, micystasia, nausea, vomiting, and pruritus (but usually disappeared in a few days with appropriate co-medication) in some patients, development of anxiety states and nightmares were attributed to opioid medication. Potency disturbances, loss of libido, amenorrhea recorded in some patients for 6-8 months after start of treatment in some cases, but these effects usually disappeared after 12 to 14 months. Treatment complications: In the 120 patients initially provided with pumps, 14 pumps had to be replaced for technical reasons (e.g. skin perforations, irregular rate of flow, pump refilling incidents, infection in vicinity of pump pocket). 25 of the 120 patients had to have pumps permanently removed for various reasons including increasing severe/intolerable side effects (6), dural leak creating therapy-resistant CSF cushion (5), physician advice or refusal to treat (4), tolerance (3), accompanying illness (3), infection (1), non-responder (1), unknown (2). |
| **Conclusions, Comments, and Quality Scores**
| Case series score: 0.5/3 Authors’ conclusions: Of the 120 patients originally enrolled, 31 (25.8%) were rated as treatment failures (e.g. insufficient reduction in pain intensity, intolerable side effects); 89/120 patients (74.2%) rated as having “proved” from continuous opioid therapy. “Our results show that the long-term therapeutic effect can be maintained for years if patients are given knowledgeable and responsible follow-up treatment. Unfavorable results or insufficient pain reduction in most cases is due to the restrictive attitude of the aftercare physician toward adequate dosage increases and the management of side effects.” Reviewer’s comments: With only 120 of 162 patients available for retrospective follow-up, if 42 unavailable patients included in final analysis, then possible that overall success rate would have been lower. Retrospective case series reliant on patient self-report. No blinding. No comparison group with either placebo treatment or standard treatment. | Study Design

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<td>162 patients initially provided with intrathecal therapy, but only 120 available for retrospective follow-up. Study based on these 120 patients with chronic, nonmalignant pain syndromes (60 males; 60 females; mean age 54.0, range 28-79). 5/82 had neuropathic pain after peripheral nerve irritation.</td>
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