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Review

Intrathecal pumps for giving opioids in chronic pain: a systematic review

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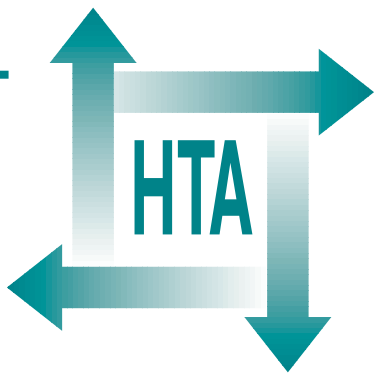

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Intrathecal pumps for giving opioids in chronic pain: a systematic review

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The NHS R&D Health Technology Assessment (HTA) Programme was set up in 1993 to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and provide care in the NHS.

Initially, six HTA panels (pharmaceuticals, acute sector, primary and community care, diagnostics and imaging, population screening, methodology) helped to set the research priorities for the HTA Programme. However, during the past few years there have been a number of changes in and around NHS R&D, such as the establishment of the National Institute for Clinical Excellence (NICE) and the creation of three new research programmes: Service Delivery and Organisation (SDO); New and Emerging Applications of Technology (NEAT); and the Methodology Programme.

This has meant that the HTA panels can now focus more explicitly on health technologies ('health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care) rather than settings of care. Therefore the panel structure has been redefined and replaced by three new panels: Pharmaceuticals; Therapeutic Procedures (including devices and operations); and Diagnostic Technologies and Screening.

The HTA Programme will continue to commission both primary and secondary research. The HTA Commissioning Board, supported by the National Coordinating Centre for Health Technology Assessment (NCCHTA), will consider and advise the Programme Director on the best research projects to pursue in order to address the research priorities identified by the three HTA panels.

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The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for any recommendations made by the authors.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The editors and publisher have tried to ensure the accuracy of this report but do not accept liability for damages or losses arising from material published in this report. They would like to thank the referees for their constructive comments on the draft document.

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Contents

List of abbreviations i

Executive summary iii

1 Background 1
Introduction 1
Aim of the review 1
Chronic pain and pain clinics 1
Treatment of chronic pain using clinical ladders and algorithms 1
Pain resistant to conventional therapies 1
Early developments in the use of intrathecal opioids 1
Spinal cord as an analgesic target 2
Mechanism of action of intrathecal opioids 2
Use of intrathecal co-analgesics 2
Pump systems for delivering intrathecal opioids 2
Clinical role 2

2 Hypotheses tested in the review 5
Research questions 5

3 Review methods 7
Search strategy for identification of studies 7
Results of the search 7
Problems with the data 7
Excluded studies 8

4 Results of the review 9
Intrathecal drugs used, doses and dose escalation 9
Efficacy 13
Risks 19

5 Costs 37
Evidence on costs and comparative costs from published studies 37

6 Analysis of the robustness of the results 39
Type of evidence found in the literature 39
Analysis of "low-grade" evidence 39
Conclusions 40

7 Opinions on the efficacy of intrathecal pump systems: responses to a telephone survey 41
Need for a telephone survey of UK "experts" 41
Sample 41
Semistructured questionnaire 41
Results 42
Conclusions 45

8 Discussion and conclusions 48
Implications for health care 48
Recommendations for further research 48

Acknowledgements 49

References 51

Health Technology Assessment reports published to date 57

Health Technology Assessment Programme 63

List of abbreviations

CSF	cerebrospinal fluid
DADL	D-Ala^2 D-Leu^5 enkephalin
MPQ	McGill Pain Questionnaire
MPQ-s	McGill Pain Questionnaire sensory subscale
NSAID	non-steroidal anti-inflammatory drug
PRI	pain rating intensity
VAS	visual analogue scale

Executive summary

Background

The use of intrathecal pumps for giving opioids in the treatment of chronic pain first started in the late 1970s. At that time it was appreciated that the spinal cord was important in pain transmission and that targeting the delivery of opioids directly to the spinal cord by using implanted intrathecal pumps could result in better pain control.

Throughout the 1980s and 1990s there were improvements in intrathecal drugs and pump systems. A wide variety of systems were in use, ranging from the simple catheter to the more sophisticated and expensive totally implantable, externally programmable pump. They were used for cancer and non-cancer patients who had pain that was resistant to conventional therapy. The aim was better pain control with fewer adverse effects than conventional routes of opioid administration such as tablets or injections. Throughout this time a wide body of clinical experience was reported in the literature.

This type of treatment is invasive, prone to side-effects and complications, costly and requires a large amount of technical support. However, there are some patients in whom all conventional pain-relieving therapies have failed and in whom this type of treatment may be beneficial.

Objectives

This review aims to answer the following questions about intrathecal pump systems, based on an analysis of the published literature.

- 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?

Methods

Studies for inclusion in the review were obtained from standard medical databases and reference lists. All studies assessing the use of intrathecal pump systems in the treatment of chronic pain were included.

Results

- A total of 114 studies, containing information on over 2000 patients, were identified.
- No randomised controlled studies or comparator studies were found. Data were extracted from case reports and case series-type information.
- The most commonly used intrathecal drug was morphine, followed by morphine in combination with bupivacaine. Dose escalation is an issue with this therapy, with reported dose increases of between 1% and 160% per week.
- A total of 53 studies were found that presented data on the effectiveness of pump systems. Sixteen of these reported visual analogue scores before and after pump usage. Average scores declined from 7.6/10 to 3/10 over a variable period of up to 2 years. All other measures of effectiveness, including various quality of life indicators, invariably reported positive effects.
- Risks of the therapy include pharmacological side-effects attributable to the drugs used (incidence 3–26% of patients) and mechanical complications associated with the pump delivery systems (incidence up to 20%).
- Patient selection criteria for this therapy are variously reported. The two main criteria are failure of or unacceptable side-effects from conventional therapy such as oral or subcutaneous opioids. A number of screening tests and trials of intrathecal therapy are used prior to actual pump implantation.
- The patient population receiving pumps is varied; some have cancer pain and some have non-cancer pain. Many will have tried numerous conventional treatments prior to intrathecal therapy; for others, with limited life expectancy and intractable pain, this is a "last resort therapy". Two distinct patient types can therefore be identified: those with long life expectancy, but with resistant pain; and cancer

patients with limited life expectancy and intractable pain that is resistant to all other treatments.
- Costs and comparative costs are not widely reported. Some information from cost modelling and projections may indicate that the cost of this treatment is comparable or advantageous when compared with existing therapies, but this depends on individual patient circumstances.
- Opinions sought from 18 UK pain specialists revealed a split in opinion over the use of these pumps in clinical practice, with one-third being in favour of their use, one-third against and one-third undecided. This non-random sample contrasted with the generally positive reports in the published literature.

Conclusions

No randomised, controlled or comparator data were found while carrying out this review. All information is therefore suboptimal. Published reports frequently use non-standard outcome measures on a heterogeneous patient population receiving different types of intrathecal pumps and drugs over varying periods. These variables make analysis very difficult. However, such data as are available indicate a generally positive effect of the therapy, with side-effects and complications occurring in about a quarter of the recipients, but it is difficult to draw definite conclusions because the quality of the data is so poor. Furthermore, the important clinical question: "Is this therapy any better than existing treatments?" is not answered by this review because of the lack of comparator data. The opinions from UK experts were not of such an overwhelmingly positive nature as the published reports.

Recommendations for research

Further research is required to establish the place of this modality in the context of existing conventional treatments; a large multicentre randomised comparator trial could be used to assess the efficacy of intrathecal therapy compared with conventional therapies in the first group of patients noted above. A database or registry of intrathecal pump usage needs to be established to gather basic information collected when utilising standardised outcome measures for pumps used in patients in the second category, in whom randomisation may be inappropriate.

Chapter 1

Background

Introduction

The use of intrathecal pump systems for administering opioids in chronic pain has developed from an understanding of the role of the spinal cord in modulating and processing nociceptive information. The delivery of opioids to this analgesic target organ using intrathecal pump systems was first achieved in 1979. Since then there have been developments in drugs and pump technology for intrathecal use. The potential advantages of intrathecal pumps include:

- Effective pain control can be achieved by delivering opioids directly to the spinal cord.
- A lower milligram dosage of opioid is required compared with systemic administration, with concomitantly fewer side-effects.
- Analgesia can be achieved in patients with previously intractable pain.
- Dosage adjustments are possible to meet changing patient needs.
- It is a reversible, non-destructive treatment.

Aim of the review

The aim of this systematic review was to collect all the available evidence on the use of intrathecal pump systems for administering opioids in patients with chronic pain, drawing conclusions concerning the effectiveness, side-effects and cost-effectiveness of the different systems currently in use, and making comparisons with existing treatments in order to determine their role in modern clinical practice.

Chronic pain and pain clinics

The establishment of pain clinics over the past 50 years has helped to focus attention on the use of different therapeutic modalities in the treatment of chronic pain. These modalities, such as drugs, nerve blocks and psychological and physical therapies, attempt to address the many facets of chronic pain.[1]

Treatment of chronic pain using clinical ladders and algorithms

Guidelines in the form of treatment ladders have emerged for the management of cancer and non-cancer pain. They include commencing treatment with mild analgesic tablets such as non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol before moving on to weak opioids and then to strong opioids.[2,3]

Pain resistant to conventional therapies

The problem, which this review addresses, is the management of those patients who have resistant pain problems or unacceptable side-effects from the use of high-dose opioids delivered by conventional routes. The precise proportion of patients who fall into one of these two groups is disputed, with reports describing an incidence of between 1% and 20% of all patients.[3–5] It is this patient group in whom it may be appropriate to use intrathecal pump systems for giving opioids. The potential is the provision of better analgesia with fewer adverse effects.

Early developments in the use of intrathecal opioids

The recognition of spinal opioid receptors led to the possibility of using the intrathecal route to provide more effective treatment of pain. That stage was reached as a result of a number of significant developments (*Table 1*).[6–8]

TABLE 1 *Developments in the use of intrathecal opioids*

Year	Development
1973	Identification of opioid receptors in the central nervous system[6]
1976	Animal studies demonstrated that intrathecal opioids produce powerful and highly selective analgesia[7]
1977	Radiolabelled opioid binding sites localised in the dorsal horn[8]

Spinal cord as an analgesic target

The spinal cord was previously considered as a relay system acting to speed the transmission of afferent and efferent information across simple reflex arcs. Over the past 20–30 years new evidence has emerged that the spinal cord is a far more dynamic organ, with its own antinociceptive pathways involving opioid neurotransmitter systems.[9] One clinical application of these discoveries was demonstrated in 1979 by Wang, who used spinally administered opioids to treat cancer pain successfully.[10]

Further studies using neuraxially administered pethidine in postoperative pain led Cousins to coin the phrase "selective spinal analgesia", whereby epidurally administered opioids could produce a specific antinociceptive block without any motor, sensory or autonomic side-effects.[11] It was subsequently demonstrated that the analgesic effect was due to the uptake of the opioid directly into the spinal cord and cerebrospinal fluid, not by systemic blood-borne effects.[12] Further use of intrathecal opioid therapy led to the recognition of side-effects of this route of delivery and the requirement to add other drugs such as local anaesthetics and alpha-2 agonists to provide effective analgesia.[13,14]

Mechanism of action of intrathecal opioids

Intrathecal opioids exert their effect by a number of different actions including the dose-dependent presynaptic inhibition of neurotransmitter release from small primary afferents, combining with hyperpolarisation of postsynaptic neurones to suppress the nociceptive stimulus.[14]

The advantage of intrathecally delivered opioids is that much lower dosages are required compared with systemic or parenteral opioid administration. The oral–parenteral:epidural–intrathecal ratio for morphine is of the order of 300–100:10–1.[4] With lower dosages required to produce the same amount of analgesia it is anticipated that side-effects will be less. However, there are practical difficulties, specific side-effects and costs associated with intrathecal delivery that make this type of therapy appropriate only after other routes have been tried.

Use of intrathecal co-analgesics

The emerging appreciation of the complexity of pain transmission mediated and modulated by the spinal cord has led to the introduction of intrathecal co-analgesics for the treatment of malignant and non-malignant pain. In particular, local anaesthetic drugs such as bupivacaine and the alpha-2 agonist, clonidine, have been widely used. The potential is for improved analgesia and for an "opioid-sparing" effect.

Pump systems for delivering intrathecal opioids

Many different pump systems for delivering opioids in chronic pain have been developed over the past 20–30 years.[15] These implantable systems were originally developed for the delivery of heparin, insulin and chemotherapeutic agents. In the late 1970s they began to be used for the administration of opioids in chronic pain. Implantable pumps accomplish drug delivery by a variety of means (*Table 2*). Some require an external driving mechanism (types 1 and 2) and others have an implanted driving mechanism (types 4 and 5). One pump (type 3) is totally implanted and is driven by externally applied intermittent manual pressure. It is anticipated that pharmacological and technological advances in the latest pumps may show a significant improvement in efficacy, with a more acceptable side-effect profile.

TABLE 2 *Intrathecal pump systems for delivering opioids*

Type	Characteristics
1	Percutaneous intrathecal catheter systems (e.g. Portex catheter) with or without subcutaneous tunnelling
2	Totally implanted intrathecal catheter with subcutaneous injection port (i.e. access port; e.g. PortaCath)
3	Totally implanted intrathecal catheter with implanted manually activated pump (pulsatile) (e.g. Algomed)
4	Totally implanted intrathecal catheter with implanted infusion pump (e.g. Infusaid)
5	Totally implanted intrathecal catheter with implanted programmable infusion pump (e.g. Synchromed)

Clinical role

The ultimate arbiter of the clinical role is the risk–benefit ratio, with the aim being better analgesia with fewer side-effects. Numerous reports have outlined the benefits and risks of intrathecal

pump systems in cancer and non-cancer pain. However, the studies are of variable quality, consisting of case reports on small numbers of patients, with heterogeneous patient selection, no controlled data, and non-standardised outcome measures.[16–18]

This review of published studies concerning intrathecal pump systems attempts to reconcile effectiveness and comparative effectiveness with side-effects and costs, and to make comparisons with existing treatments to place this therapy properly in modern clinical practice.

Chapter 2

Hypotheses tested in the review

There are a number of questions to be answered when assessing the validity of a particular therapy or intervention; not least of these is the question of effectiveness or efficacy: does the therapy work? Effectiveness should not be assessed in isolation. It may well be effective but it needs to be assessed in comparison with other therapies. Further considerations focus on how appropriate it is compared with existing treatments, what the risks are in relation to the perceived benefits and, finally, other relevant factors, such as repercussions on quality of life and issues of costs.

Research questions

- Drugs used
  - What intrathecal drugs and dosages have been used?
  - To what extent is dose escalation an issue in intrathecal therapy?
- Efficacy
  - How effective are intrathecal pump systems for giving opioids in chronic pain?
  - How effective are they compared with conventional routes of opioid delivery?
- Side-effects/risks (this section has been divided into: (a) pharmacological side-effects of drugs given intrathecally; and (b) technical complications of the pump delivery systems)
  - What are the risks associated with this type of therapy?
  - What is the incidence of pharmacological adverse effects, such as respiratory depression?
  - What is the risk of complications such as meningitis and pump delivery system failure?
- Selection criteria
  - What patient selection criteria have been used for intrathecal therapy?
- Costs and comparative costs
  - What are the costs and comparative costs of intrathecal therapy?

Chapter 3

Review methods

Search strategy for identification of studies

Electronic searches were conducted in MEDLINE, EMBASE, CancerCD and PubMed. Studies were sought that included information on the patient population, interventions and outcomes. 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)
- Interventions
  - different types of intrathecal pump systems for giving opioids in chronic pain control (pump types 1–5; *Table 1*)
  - 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, intramuscular, intravenous, transdermal, intraventricular, neuroablative, neurolytic and neurosurgical interventions
- Outcomes
  - efficacy measures included: 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, pruritus); and (b) complications (e.g. local infection, abscess formation, meningitis, bleeding/haematoma formation, pump pocket seroma, cerebro spinal fluid (CSF) leaks, dural fistula, improper pocket placement, catheter kinking, catheter obstruction, catheter dislodgement, catheter disconnection, catheter malfunction, pump failure)
  - costs: (a) costs of intrathecal pump systems, including initial costs, maintenance, number of outpatient visits, hospital admissions and use of health care resources; and (b) financial benefits of the pump systems, such as reduction in drug costs, reduction in bed days, quicker return to work, reduction in the use of health service resources (GP visits, outpatient visits).

Results of the search

- Electronic database searching initially produced 5764 studies that mentioned the use of intrathecal opioids. Further reading of these reports revealed that only 49 actually assessed the efficacy of intrathecal pump systems for delivering opioids in chronic pain.[19–67]
- Other studies were identified that provided information on intrathecal therapy, such as side-effects, complications, costs and patient selection criteria, but did not specifically measure efficacy.[13, 68–101]
- Studies containing information on intrathecal therapy, but which were not used in this review, are also listed.[102–128]
- None of these studies were randomised controlled trials or compared the effectiveness of intrathecal pump systems with other analgesic methods.
- Both case series (studies containing more than one patient) and case reports (studies on single patients) are included in this review.
- Studies assessing the effectiveness of the intraventricular administration of opioids are also included.

Problems with the data

- When assessing the effectiveness of an intervention it is not valid simply to measure a post-intervention score. Studies should address the **changes** that take place rather than simply present a static post-intervention snapshot purporting to show efficacy. Only a quarter of all the studies (case series and case reports) attempted to measure the change induced by the therapy.
- Whereas a systematic review differs from other reviews by methodically ensuring that all studies meeting the inclusion criteria are included, this review, because of the nature of the evidence, has not necessarily included every existing case study or case series. The rationale for this is that the low-quality evidence adds neither weight nor novelty to the review itself.

In addition, adverse effects and complications have not been utilised from case reports because they do not include a denominator of cases and would therefore bias the evidence even more severely.

Excluded studies

- review articles with no original information
- studies assessing the effectiveness of epidural therapy only.
- Not all case-series reports have been included in the data analysis. This is because many of the reports did not provide sufficient information on effects and side-effects. The percentage figures for side-effects therefore apply only to the studies that have been included in the analysis.

Chapter 4

Results of the review

Intrathecal drugs used, doses and dose escalation

Drugs used

The most commonly used drug, by a considerable degree, is morphine. A total of 1672 patients in the studies included in this review were given morphine as a single agent. Morphine and bupivacaine were given to 532 patients, and morphine in conjunction with other drugs was prescribed for a further 175 patients (94 received morphine, bupivacaine and buprenorphine). *Table 3* lists all the intrathecal drugs used, together with the total numbers of patients receiving them.

Dose escalation

Dose escalation has been reported in the use of intrathecal opioids but it is often not clear whether this was owing to disease progression or clinicians starting with a low dose, or to the development of true spinal tolerance.

Portenoy and Savage[96] used a variety of ways to describe tolerance. They wrote of "associative tolerance" and described it as "a diminution in effect that occurs as a result of learning". They also used the term "pharmacologic tolerance" and classified it as "dispositional or pharmacodynamic". Dispositional tolerance "describes a reduction in drug effect due to pharmacokinetic changes". Pharmacodynamic tolerance refers to "a reduction in effect secondary to changes in neural systems rather than to changes in drug disposition".

The mechanism of tolerance is not yet understood, however, cross-tolerance appears to exist between narcotic agents and between systemic and spinal opioids.[50]

The lack of controlled data hinders effective consideration of these issues. The optimum review would show data comparing dose escalation in relation to efficacy and adverse effects. The variability of data, populations and conditions in the studies included in this review disallows this. Some studies provided just one dose, either the first or the last, while others presented information that enabled us to assess dose escalation.

Table 4 shows the escalation of morphine doses in eight studies that provided enough information to enable us to calculate average values. To produce a figure showing average dose escalation we have derived a value called "average dose escalation per week". This assumes that there is a linear relationship between time and response,

TABLE 3 *Numbers of patients receiving specific intrathecal drugs*

Drugs used	Total no. patients receiving drug(s)
Morphine	1672
Morphine + bupivacaine	532
Morphine + bupivacaine + buprenorphine	94
Bupivacaine + buprenorphine	55
Bupivacaine	52
Morphine and/or clonidine, calcitonin, bupivacaine	33
Fentanyl + lidocaine	24
Morphine + ketamine	20
Morphine + sufentanil	18
DADL	12
Fentanyl	8
ß-Endorphin + dynorphin	7
Dynorphin	6
Sufentanil	6
ß-Endorphin	5
Buprenorphine	5
Morphine + bupivacaine + clonidine	5
Hydromorphone	3
Methadone	3
Morphine + octreotide	3
Clonidine	2
Morphine + clonidine	2
Bupivacaine + pethidine	1
Diamorphine	1
Dilaudid	1
Lidocaine	1
Total	2571

DADL, D-Ala^{2}D-Leu^5 enkephalin

TABLE 4 *Dose escalation in studies using intrathecal morphine (all numbers are means); only studies providing accurate first and final dose information are included*

Reference	No. patients	First dose (mg/day)	Final dose (mg/day)	Time (weeks)	Dose escalation (mg/week)	Average % dose increase/week
Anderson and Burchiel, 1999[19]	30	2	14	103	0.12	7
Cheng *et al.,* 1993[24]	100	0.2	1.4	12	0.1	60
Gestin *et al.,* 1997[33]	50	2.5	9.2	33	0.2	11
Krames *et al.,* 1985[39]	17	3.3	32.3	20	1.5	48
Maeyaert and Kupers, 1996[85]	28	0.35	2.5	64.5	0.03	3.3
Mercadante, 1994[43]	15	2	4.2	2.2	1	95
Shetter *et al.,* 1986[57]	8	4.5	18	2.5	5.4	160
Winkelmuller and Winkelmuller, 1996[65]	88	2.7	4.7	176.8	0.01	0.9

which is a difficult assumption to make. Tutak and Doleys,[60] for example, suggest that the curve during the initial period is steeper than that later in the treatment, thus negating this assumption. They state that: "There appeared to be a positively accelerating curve up to 15 months after implantation of the pump, followed by a decrease in the rate of acceleration from 15 to 21 months." The figures are presented, therefore, with caution and an exhortation to view the results in full. The average dose escalations per week varied between < 1% and 160% in the studies listed in *Table 4*.

Table 5 shows information on dose escalation in other studies. All these authors reported dose escalation of varying degrees but usually of the order of 25% per week.

TABLE 5 *Further details of dose escalation reported in other studies*

Reference	No. patients	Trial design	Drug	Initial dose	2nd period dose	Final dose	Notes
Bloomfield *et al.,* 1995[20]	50	Case series	Morphine			< 10 mg/day in 20% (*n* = 10) Dose escalation of 10–35 mg/day in 24% (*n* = 12)	5 patients (10%) had "true tolerance"
Brazenor, 1987[22]	25	Case series	Morphine	0.25 mg/12 h 1.5 mg/12 h after 14 days	***Maintenance doses*** 0.25–8 mg/day in patients with reservoirs 1–15 mg/day in patients with pumps	Some patients with a reservoir required up to 50 mg/day Some patients with a pump required up to 75 mg/day	Patients remained in hospital 14 days postoperatively
Chambers and MacSullivan, 1994[23]	15	Case series	Morphine	Usually 2–3 mg/day		4–40 mg/day	
Cobb et al., 1984[25]	10	Case series	Morphine			2–4 mg/12–24 h	Initial daily dose calculated: oral/300
Coombs *et al.,* 1984[27]	6	Prospective case series	Morphine			0.5–75 mg/day	Dosages were escalated if increased pain reports persisted > 2 days
Devulder *et al.,* 1994[30]	33	Case series	Morphine; some patients also + clonidine, calcitonin or bupivacaine			< 5 mg/day (*n* =3) 5–10 mg/day (*n* = 7) 10–50 mg/day (*n* = 13) > 50 mg/day (*n* = 1)	

continued

TABLE 5 contd *Further details of dose escalation reported in other studies*

Reference	No. patients	Trial design	Drug	Initial dose	2nd period dose	Final dose	Notes
Follett *et al.*, 1992[31]	37	Case series	Morphine	Mean 5.4 mg/day		± 10 mg/day (extracted from graph)	62% (*n* = 23) increased dose 27% (*n* = 10) stable dose 11% (*n* = 4) reduced doses Dose escalation common in first 4–8 weeks
Hardy and Wells, 1990[36]	8	Case series	Morphine	1 mg with lock-out of 30 min		2–30 mg/day Mean 12.6 mg/day	Stable demand pattern established after 24 h – bolus calculated on this
Hassenbusch *et al.*, 1995[37]	18	Prospective case series	Morphine + sufentanil	159% ± 27% less than final follow-up dose for successful patients 371% ± 112% less than final follow-up dose for unsuccessful patients		Morphine 14–19 mg/day Sufentanil 12–24 µg/day Morphine 34–53 mg/day Sufentanil 34–72 µg/day	
Lazorthes *et al.*, 1985[40]	52	Case series	Morphine			Mean 2.5 mg/day Range 1–10 mg/day	
Lipman and Blumenkopf, 1989[41]	5	Case series	Morphine	1–2.25 mg/day			
Madrid *et al.*, 1988[42]	100	Case series	Morphine		2–4 mg/day at 2 months	Up to 6 mg/day at 7 months	
Muller *et al.*, 1988[44]	23	Case series	Morphine			8.3 mg/day	
Nitescu *et al.*, 1998[45]	90	Prospective cohort	Morphine ± bupivacaine Buprenorphine ± bupivacaine			***Nociceptive pain*** Morphine mean 2.6 mg/day Buprenorphine mean 31 mg/day ***Neuropathic pain*** Morphine 5 mg/day Buprenorphine 46 mg/day ***Mixed pain*** Morphine 2.8 mg/day Buprenorphine 35 mg/day	
Paice, 1986[50]	4	Case series	Morphine			1.5–100 mg/day Mean 26 mg/day	
Paice *et al.*, 1996[48]	429	Survey	Many different opioids			Mean 2–14 mg/day	
Penn *et al.*, 1984[54]	12	Case series	Morphine			***Pump type 4*** 1.5–8 mg/day (mean 4.9) ***Pump type 5*** 0.2–10 mg/day (mean 2.96)	
Penn and Paice, 1987[53]	43	Case series	Morphine				Typically, dose doubled by time patient died (usually 3–9 months)

continued

TABLE 5 contd *Further details of dose escalation reported in other studies*

Reference	No. patients	Trial design	Drug	Initial dose	2nd period dose	Final dose	Notes
Schultheiss *et al.*, 1992[56]	79	Case series	Morphine			Dose increases reported	Mean survival 80–100 days
Sjoberg *et al.*, 1991[59]	52	Prospective case series	Morphine + bupivacaine	1–2.5 mg/day each		1–15 times/day (median 5) with injections (n = 24)	Morphine increased when side-effects from bupivacaine Bupivacaine increased when pain not relieved
Sjoberg *et al.*, 1994[58]	53	Case series		Bupivacaine 30–45 mg/day during first 2 weeks	Morphine 3–10 mg/day (20–40 mg/day in 7 patients) Bupivacaine > 45–60 mg/day next 3 months	Morphine 60 mg/day during 5th and 6th months Bupivacaine > 60–90 mg/day next 2 months	
Tutak and Doleys, 1996[60]	26	Case series	Morphine Morphine + bupivacaine	3 months post-implantation mean 1.38 mg/day	***6 months post-implantation*** Mean 2.47 mg/day ***12 months post-implantation*** Mean 5.49 mg/day ***18 months post-implantation*** Mean 8.79 mg/day	***21 months post-implantation*** Mean 9.34 mg/day	
van Dongen *et al.*, 1993[61]	51	Case series	Morphine + bupivacaine	1/60th of oral daily morphine intake Morphine 1 mg/day + bupivacaine 2–4 mg/day		Morphine 1–33 mg/day (mean 8) Bupivacaine 10–100 mg/day (mean 31)	
Ventafridda *et al.*, 1987[62]	18	Case series	Morphine	≈ 1 mg/day at 1 week (data taken from graph)	≈ 2.5 mg/day at 6 weeks	≈ 15 mg/day at 16 weeks	
Wagemans *et al.*, 1997[99]	10	Case series	Morphine Bupivacaine (4 patients)			Morphine 2.75–30.25 mg/day Bupivacaine 5.63–91.24 mg/day	
Wang, 1985[63]	62	Case series	Morphine	0.5–2.0 mg	24 patients did not experience tolerance		Morphine was ineffective in 26% of patients
Yang *et al.*, 1996[66]	20	Prospective randomly assigned, double-blind cross-over study	Morphine Morphine + ketamine			Some dose escalation reported	

Table 6 outlines dose escalation in two studies in which intraventricular opioids were used.

Efficacy

The data were analysed in three different ways:

- measurement of effectiveness by combining VAS pain scores
- assessment of "evidence for improvement"
- assessment of non-VAS pain scores.

Measurement of effectiveness by combining VAS pain scores

Sixteen studies assessing the efficacy of intrathecal therapy presented both pre- and post-therapy VAS scores, which allowed for comparison (*Table 7*).

Differences in study size were accounted for by multiplying the mean score by the number of patients. These numbers were combined and averaged to obtain pre- and post-therapy mean VAS scores. The results showed a substantial drop in pain score from 7.6 pre-therapy to 3.0 post-therapy.

However, it is essential to be aware of the inherent problems when combining the results of these studies because the variables involved are not matched. The patient populations and types of intervention (pump type and drug type) are not necessarily equivalent. In addition, the drug dosing schedules are not necessarily similar, follow-up periods may be different, and additional, potentially confounding factors are not redressed.

TABLE 6 *Dose escalation in studies using the intraventricular route of administration*

Reference	No. patients	First dose (mg/day)	Final dose (mg/day)	Time (weeks)	Mean escalation (mg/week)	Average % dose increase/week
Lenzi *et al.*, 1985[81]	38	0.64	1.04	10.6	0.4	4
Lobato *et al.*, 1983[83]	17	0.77	2.64	7.5	1.87	25

TABLE 7 *Comparison of 16 studies that assessed pre- and post-intervention VAS scores (out of 100)*

Reference	No. patients	Pre-therapy VAS score	Post-therapy VAS score	Pre-therapy VAS score X no. patients	Post-therapy VAS score X no. patients
Anderson and Burchiel, 1999[19]	30	78.5	58.5	2,355	1,755
Borg and Krijnen, 1996[21]	4	7	1	28	4
Chambers and MacSullivan, 1994[23]	15	80	20	1,200	300
Coombs, 1986[26]	1	9	5	9	5
Crul *et al.*, 1994[29]	2	7	1	14	2
Hassenbusch *et al.*, 1995[37]	18	81	66	1,458	1,188
Jin *et al.*, 1986[38]	2	7	1	14	2
Nitescu *et al.*, 1998[45]	90	65	12.5	5,850	1,125
Parker *et al.*, 1987[51]	12	39	31	468	372
Penn *et al.*, 1992[52]	1	10	0	10	0
Sjoberg *et al.*, 1991[59]	52	68.5	25	3,562	1,300
Sjoberg *et al.*, 1994[58]	53	89	10	4,717	530
Tutak and Doleys, 1996[60]	26	89	55	2,314	1,430
Ventafridda *et al.*, 1987[62]	18	12	5	216	90
Winkelmuller and Winkelmuller, 1996[65]	120	95	39	11,400	4,680
Yang *et al.*, 1996[66]	20	79.5	22	1,590	440
Average – rounded on a 10-point scale				7.6	3

Assessment of "evidence for improvement"

A further 27 studies used VAS pain scores, but in these pain was measured only **after** pump implantation (*Table 8*).

We decided to use an assessment showing evidence of improvement based on the authors' claim that there was an improvement as a result of the intervention. Using this measure does not lay great claims; it is simply a somewhat nebulous way of

TABLE 8 *Details of studies measuring VAS pain scores* ***after*** *pump implantation*

Reference	Pump type(s)	No. patients	Patient type	Post-therapy pain relief
Bloomfield *et al.*, 1995[20]	4 and 5	50	Non-cancer	78% > 50% pain reduction
Brazenor, 1987[22]	3 and 4	26	23 cancer 3 non-cancer	73% excellent[a]
Cheng *et al.*, 1993[24]	2	100	Cancer	9% comfortable[b]
Cobb *et al.*, 1984[25]	2	10	Cancer	Pain relief for 24 h
Coombs *et al.*, 1984[27]	4	6	Cancer	VAS score 4.2 at 2 months
Coombs *et al.*, 1983[28]	4	2 intrathecal 8 epidural	5 cancer 5 non-cancer	Intrathecal data mixed with epidural
Devulder *et al.*, 1994[30]	1	10 bolus 23 pump	Cancer	50% good[c] 87%[d,e]
Follet *et al.*, 1992[31]	4	37	35 cancer 2 non-cancer	77% good[f]
Gestin *et al.*, 1997[33]	1	50	Cancer	Mean VAS 3.9[g]
Gourlay *et al.*, 1991[34]	2 and 4	10	Cancer	Mean VAS 1.45[h]
Hanna *et al.*, 1990[35]	1	3	Cancer	Absent or mild
Hardy and Wells, 1990[36]	2	8	Cancer	Good analgesia
Krames *et al.*, 1985[39]	4	11 intrathecal 6 epidural	16 cancer 1 non-cancer	Mean 2.72[i]
Lazorthes *et al.*, 1985[40]	1 and 5	52 spinal 18 intraventricular	Cancer	81% good–excellent[j]
Lipman and Blumenkopf, 1989[41]	1	5	Chronic pain	Some pain relief recorded as measured by visual analogue scale
Madrid *et al.*, 1988[42]	2	100	Cancer	28% controlled their pain
Muller *et al.*, 1988[44]	4	23	Cancer	1–4[k]
Nitescu *et al.*, 1991[47]	1	142	Cancer	0–2[l]
Paice, 1986[50]	4	17	Cancer	94% said pump had made positive impact
Paice *et al.*, 1996[48]	5	429[m]	32.7% cancer 67.3% non-cancer	61% ± 1.35%
Penn *et al.*, 1984[54]	4 and 5	12	Cancer	0 (n = 2), 4–6 (n = 3) 2–3 (n = 4), 4–6 (n = 2)[n]
Penn and Paice, 1987[53]	4 and 5	43	35 cancer 8 non-cancer	80% good–excellent[o]
Schultheiss *et al.*, 1992[56]	2 and 4		Cancer	60–80% decrease in pain
Shetter *et al.*, 1986[57]	4	7	Cancer	72% excellent 14% good 14% poor[p]

continued

TABLE 8 contd *Details of studies measuring VAS pain scores* ***after*** *pump implantation*

Reference	Pump type(s)	No. patients	Patient type	Post-therapy pain relief
Sjoberg *et al.*, 1991[59]	1 and 2	52	Cancer	2 (*n* = 44/52) 3–8 (*n* = 8/52)
van Dongen *et al.*, 1993[61]	1	51	Cancer	59% good[q]
Wang, 1985[63]	Single shot, 1 and 4	62	Cancer	74% responded with reduced pain[r]

[a] *Patients and relatives rated pain relief as excellent*
[b] *Pain level at 12 weeks: 9% comfortable, 52% weak, 28% mild, 7% moderate, 4% severe*
[c] *Bolus*
[d] *Continuous*
[e] *VAS score: ≤ 3 = good analgesia, > 5 = inadequate*
[f] *< 2–3 on 10-point scale*
[g] *10-point scale*
[h] *Intrathecal data mixed with epidural data*
[i] *5-point scale*
[j] *i.e. 81% of patients had 50–100% analgesia*
[k] *1.3 at start; 1.4 after 1 month; 1.5 at final stage. 4-point score: 1 = excellent pain reduction; 4 = poor pain reduction*
[l] *In most patients 0–10-point scale*
[m] *This was a survey of physicians and patients*
[n] *10-point scale*
[o] *Excellent = 0–3 on 10-point scale: > 50% reduction in oral narcotics and some improvements in daily activities. Good = 4–6: <50% reduction in oral narcotics and some improvements in daily activities. Poor = 7–10: slight decreases in oral narcotics and little change in activities. Failure = no pain relief, continuing need for oral narcotics and no change in activities*
[p] *Excellent = pain reduction > 75%, supplemental narcotic usage < 3.5 parenteral morphine equivalents per day. Good = > 50% pain reduction, supplemental narcotics required but no further treatment for pain. Fair = < 50% pain reduction, supplemental narcotics required but no further treatment. Poor = < 25% pain reduction, supplemental narcotics required and further hospitalisation or treatment needed*
[q] *Relates to the 17 patients who had morphine and bupivacaine. Good = patients needed no or only incidental concomitant analgesia on a regular basis or pain persistent during movement. Poor = pain present despite regular administration of analgesia*
[r] *Responded with reduced pain; 26% failed to obtain satisfactory pain relief or experienced intolerable complications*

showing an element of evidence. Those studies showing evidence of improvement were often difficult to quantify and impossible to combine.

All 27 studies showed some evidence of improvement after the use of intrathecal pumps.

Assessment of non-VAS pain scores

Other objective measures of pain relief were used. A summary is outlined in *Table 9*.

TABLE 9 *Effectiveness as indicated by other objective measures*

Measure used	Range of effectiveness	No. studies
MPQ scores	Overall improvements	1
Use of supplemental analgesia	15–50% reduction	5
Functional assessment		
Ability to return to work	6–8% improvement	2
Good to excellent improvement in daily activities	22.3% good; 82.5% good to excellent	2
Sleep pattern	Some improvement	4
Gait	Some slight improvement in 2 out of 3 studies	3
Patient satisfaction/acceptability	77–92% improvement	2
Depression and psychometric tests	Improvement	1
Miscellaneous tests	Overall improvement	1

MPQ scores

Anderson and Burchiel,[19] in a prospective series of 20 non-malignant pain patients who were receiving intrathecal opioid infusions and were followed up for 2 years, assessed pain using the MPQ and VAS. All VAS scores throughout the 2-year period showed significant improvement (25% improvement, $p < 0.05$). MPQ scores were reported as follows (*Table 10*):

- MPQ, pain rating intensity (PRI): The results showed a significant improvement in the overall PRI after 3 months. This was sustained for 18 months but reduced slightly after 24 months from the beginning of therapy.
- Individual sensory subscale of the MPQ (MPQ-s): There was immediate improvement, sustained over 18 months, and a return to baseline levels in the final 6 months.

TABLE 10 *Pain rating scores from Anderson and Burchiel, 1999*[19]

Pain Measure	Initial pain score	3 months	6 months	12 months	18 months	24 months
PRI	36	24*	24*	25*	26*	30*
MPQ-s	20	14*	15*	16*	16*	18

$p < 0.05$ (>25% improvement in pain scores)

- Individual affective subscale of the MPQ (MPQ-a): No significant change.
- Individual evaluative subscale of the MPQ (MPQ-e): No significant change.

Use of supplemental analgesia

The authors of six of the seven articles that included the use of supplemental analgesia as an outcome measure reported a convincing decrease in both the number and quantity of supplementary analgesics used. These were both opioids and non-opioids (*Table 11*).

TABLE 11 *Supplemental analgesia usage after pump implantation*

Reference	Outcome
Brazenor, 1987[22]	19/26 (73%) needed no additional narcotics
Hassenbusch *et al.*, 1995[37]	At last follow-up 55% (6/11) successful patients occasionally used NSAIDs, 18% (2/11) regularly used Schedule I opioids, and 27% (3/11) regularly used Schedule II opioids
Nitescu *et al.*, 1998[45]	89/90 (99%) took non-opioid and sedative drugs before treatment versus 54 (60%) during treatment; median number of drugs decreased from 2 to 1/day
Penn *et al.*, 1984[54]	Decrease by 50% (6/12)
Sjoberg *et al.*, 1994[58]	Non-opioid analgesics and sedatives[a]: mean score 2 initially; mean score 1 after pump usage
Sjoberg *et al.*, 1991[59]	25% of patients did not take non-opiate analgesics or sedative drugs during intrathecal treatment compared with 10% before
Tutak and Doleys, 1996[60]	Average daily oral morphine equivalent: decrease from 289 mg/day to 175 mg/day

[a] 0 = high daily dose of lytic cocktails; 1 = 4 drugs; 2 = 3 drugs; 3 = 2 drugs; 4 = 1 drug; 5 = no drugs

Of the six studies showing a decrease in the amount of analgesics taken, in five a percentage was assigned to that decrease. This is shown in *Table 12*. The studies have not been combined because the variables involved are too heterogeneous to allow valid aggregation.

TABLE 12 *Decrease in supplemental analgesia needed*

Reference	% decrease
Nitescu *et al.*, 1998[45]	45
Penn *et al.*, 1984[54]	50
Sjoberg *et al.*, 1994[58]	50
Sjoberg *et al.*, 1991[59]	15
Tutak and Doleys, 1996[60]	39

Functional assessment

Functional assessment is an umbrella term and covers a range of measures including multiple daily activities, functional capacity and ability to return to work since undergoing therapy (*Table 13*).

Although all studies showed some functional improvement, Anderson and Burchiel[19] provided a cautionary note when they suggested that the trend of improvement was not maintained after a 2-year interval. Brazenor[22] also noted that there was some worsening in ability as well as some improvement. However, the extent of the improvement was greater than that of the deterioration (*Table 13*).

Paice and colleagues[48] and Penn and co-workers[54] reported that 6% and 8% of patients respectively were able to return to work after therapy.

"Good to excellent" improvements in daily activities were demonstrated by Paice and co-authors[48] (22.3% good) and by Penn and Paice[53] (82.5% good to excellent).

Sleep pattern

The impact of the therapy on sleep pattern was documented in four articles (*Table 14*). This small sample suggests there is an increase in the number of hours patients are able to sleep when using intrathecal pump systems.

Yang and colleagues[66] considered sleep in relation to drug type and compared morphine with morphine plus ketamine. They found that there was less sleep deprivation with morphine and ketamine than with morphine alone.

Gait

From the evidence available (*Table 15*), it is difficult to determine either a beneficial or a detrimental effect on gait. Although the authors of one article suggested that there was a statistically significant improvement,[59] others reported that there was none.[45] A third group showed minimal improvement from 3 (could walk with crutches) to 3–3.5 on a 5-point scale.[58]

TABLE 13 *Functional assessment*

Reference	Outcome
Anderson and Burchiel, 1999[19]	Improvement through first 12 months; trend not maintained and by 24 months total scores returned to baseline
Brazenor, 1987[22]	12% (3/26) worsened by 1–2 grades; 50% (13/26) improved by 1–4 grades[a]
Cheng *et al.*, 1993[24]	Bed-ridden 24% compared with 31% prior to treatment
Hassenbusch *et al.*, 1995[37]	7.9% ± 9.0% improvement on a 100-point score[b]
Paice *et al.*, 1996[48]	Improvement: 24.6% slight, 34.3% modest, 22.3% good Return to work: 6.5% (28/429) of patients who were not working prior to implantation returned to work after initiating therapy
Parker *et al.*, 1987[51]	Performance status from hospital records and family interviews: increase by 1 grade 42% (5/12); increase by 2 grades 17% (2/12)
Penn and Paice, 1987[53]	Changes in daily living: 80% (28/35) cancer patients – good to excellent; 83.7% (36/43) non-cancer patients – good to excellent
Penn *et al.*, 1984[54]	Daily activities: all showed an increase; all able to ambulate and perform self-care; 1/12 returned to work; all able to go home
Tutak and Doleys, 1996[60]	Pre-therapy mean grade = 4; post-therapy mean grade = 2.8 (range 1–5; scale 1 best, 6 worst)
Winkelmuller and Winkelmuller, 1996[65]	Activity levels: 94% were passive and withdrawn before; 43% after

[a] 1–6 grades of functional capacity: 1 = working executive capacity; 2 = working non-executive capacity; 3 = not working but not confined to home; 4 = confined to home but not dependent; 5 = confined to home and dependent; 6 = institutionalised
[b] Activity rating: 100 job full-time; 90 job part-time; 80 drives a car ≥ 1 x per month; 70 out of house and property ≥ 2 x per month; 60 out of house and property ≤ 2 x per month; 50 out of house but not off property; 40 does household chores; 30 no household chores but out of bed ≥ 6 h/day; 20 out of bed < 6 h/day; 10 bedbound; 0 dead

Patient satisfaction/acceptability

Five articles were concerned with issues that are broadly included in this section (*Table 16*) (e.g. by the use of such terms as: a problems scale, a recommendations scale, mood levels, quality of life, satisfaction, acceptability, and life interference). Tutak and Doleys[60] assessed the views of patients and spouses, as well as those of clinical staff. They showed an interesting comparison of satisfaction levels, with only half the number of spouses rating the therapy as good to excellent compared with clinical staff.

TABLE 14 *Sleep pattern*

Reference	Outcome
Nitescu *et al.*, 1998[45]	Significant increase in duration of sleep from < 4 h before treatment to 7 h (median values) during treatment
Sjoberg *et al.*, 1994[58]	Sleep pattern[a]: mean 2 initially; subsequently mean range 3–4.5
Sjoberg *et al.*, 1991[59]	Improved significantly: half slept uninterrupted for > 4 h compared with 2 h before therapy
Yang *et al.*, 1996[66]	10-point scale of sleep deprivation: pretrial = 7.3; on the last day of the trial using morphine = 2.0; and morphine + ketamine = 1.65

[a] 0 = coma; 1 = < 2 h; 2 = > 2 h; 3 = > 4 h; 4 = > 6 h; 5 = 7–8 h

TABLE 15 *Gait*

Reference	Outcome
Nitescu *et al.*, 1998[45]	No significant difference ($p > 0.5$)
Sjoberg *et al.*, 1994[58]	Gait scale[a]: mean 3 initially, subsequently range 3–3.5
Sjoberg *et al.*, 1991[59]	Statistically significant ($p < 0.05$) improvement 4 weeks after start and thereafter

[a] 0 = bedridden; 1 = could be moved; 2 = could move independently; 3 = could walk with crutches; 4 = could walk without help; 5 = normal

TABLE 16 *Patient satisfaction/acceptability*

Reference	Outcome
Cheng *et al.*, 1993[24]	Acceptability[a]: 83% of patients "felt good" at the end of week 1;. 7% "mildly accepting"
Gourlay *et al.*, 1991[34]	***5-point categorical scale satisfaction assessments*** Pain relief mean 2.72 Problems scale mean 5.2 Recommendation scale mean 3.51[b]
Tutak and Doleys, 1996[60]	77% of patients, 55% of spouses rated it good to excellent; 100% of clinic staff rated it good to excellent
Winkelmuller and Winkelmuller, 1996[65]	Mood levels: 88% (63/72) were "isolated or depressed" compared with 13% (9/72) after therapy Quality of life: 80% improvement Satisfaction: 92% (66/72) satisfied with therapy
Yang *et al.*, 1996[66]	***10-point scale*** Life interference = 7.4 pre-trial Morphine = 2.25 last day Morphine and ketamine = 2.05 last day

[a] Acceptability was divided into the following groups according to the VAS score: none or little 0–25; mild 26–50; moderate 51–75; good 76–100
[b] Mean duration of intrathecal treatment: 127 days for infusion; 38 days for bolus

Depression and psychometric tests

In only one article were these outcome measures used. Gourlay and colleagues' study[34] used four objective and validated tests to assess depression (*Table 17*). Although this study combines both intrathecal and epidural data it is nevertheless still worth noting the results. The purpose of this study was to compare bolus versus infusion techniques. From the available evidence it shows infusion to be more effective than bolus, although this is not statistically significant. It is included in this section because it also demonstrated the use of depression and psychometric tests.

A thorough exploration of the key psychometric tests, including a discussion of their advantages and disadvantages, can be found in an article by Krames.[77]

TABLE 17 *Depression and psychometric tests (Gourlay* et al., *1991[34])*

Test	Infusion group mean	Bolus group mean
Beck Depression Inventory (↓)	9.41	10.36
Williams Delay Recall (memory) (↓)	7.03	9.88
Word recognition (vigilance) (↓)	2.06	4.20
Symbol/digit (attention and processing) (↑)	38.7	31.5
Direction of arrows indicates change that is favourable		

Miscellaneous

Although all pain rating is, by its nature, inherently subjective, some researchers make an attempt to objectify it by measuring physiological changes, such as in Lipman and Blumenkopf's study.[41] They used heat beam dolorimetry to measure pain perception and pain thresholds. They were able to show some evidence of increased cutaneous pain tolerance with the use of intrathecal therapy.

All the studies included here present a favourable outcome in terms of pain control with this therapy. Paice and co-workers[48] and Penn and colleagues[54] achieved similar results for subjective pain ratings. Paice's group presented a good to excellent result of 95.3% in 429 patients, while that for Penn's group was 92% in only eight patients.

Outcomes from other pain scores are presented in *Table 18*, and details of the pump systems used and the duration of intrathecal therapy are listed in *Tables 19* and *20* respectively.

TABLE 18 *Outcomes from other pain scores*

Reference	Outcome
Lipman and Blumenkopf, 1989[41]	Pain severity and pain relief[a]: slower onset and lesser degree than intravenous morphine infusion. Heat beam dolorimetry: heat beam dolorimetric evidence of increased cutaneous pain tolerance with intrathecal infusion
Paice *et al.*, 1996[48]	Global relief of pain: 4.8% poor, 42.9% good, 52.4% excellent
Penn *et al.*, 1984[54]	Subjective pain relief: excellent 50% (6/12), good 42% (5/12), poor 8% (1/12)
Tutak and Doleys, 1996[60]	Subjective rating improvement in pain: average 59%
Ventafridda *et al.*, 1987[62]	Integrated score[b] : significant fall in integrated score from 42 to 10

[a] Scale: none, a little, some, a lot, terrible

[b] Integrated score included: number of hours with pain referred to by five key words; number of hours' sleep; number of hours spent standing, sitting, lying; presence or absence of side-effects during the day

TABLE 19 *Details of different pump systems used*

Reference	No. patients	Trial design	Pump type
Devulder *et al.*, 1994[30]	33	Case series	1
Gestin *et al.*, 1997[33]	50	Case series	1
Hanna *et al.*, 1990[35]	3	Case series	1
Lipman and Blumenkopf, 1989[41]	5	Case series	1
Mercadante, 1994[43]	15	Prospective case series	1
Nitescu *et al.*, 1998[45]	90	Prospective cohort	1
van Dongen *et al.*, 1993[61]	51	Case series	1
Cheng *et al.*, 1993[24]	100	Case series	2
Cobb *et al.*, 1984[25]	10	Case series	2
Hardy and Wells, 1990[36]	8	Case series	2
Madrid *et al.*, 1988[42]	100	Case series	2
Sjoberg *et al.*, 1994[58]	53	Case series	2
Yang *et al.*, 1996[66]	20	Prospective randomly assigned, double-blind cross-over study	2
Sjoberg *et al.*, 1991[59]	52	Prospective case series	1, 2
Ventafridda *et al.*, 1987[62]	18	Case series	1, 2
Coombs *et al.*, 1984[27]	6	Prospective case series	4

continued

TABLE 19 contd *Details of different pump systems used*

Reference	No. patients	Trial design	Pump type
Krames *et al.*, 1985[39]	17	Case series	4
Muller *et al.*, 1988[44]	23	Case series	4
Paice, 1986[50]	4	Case series	4
Shetter *et al.*, 1986[57]	8	Case series	4
Anderson and Burchiel, 1999[19]	40	Prospective cohort	5
Chambers and MacSullivan, 1994[23]	15	Case series	5
Hassenbusch *et al.*, 1995[37]	18	Prospective case series	5
Paice *et al.*, 1996[48]	429	Survey	5
Tutak and Doleys, 1996[60]	26	Retrospective case series	5
Wang, 1985[63]	62	Case series	Single shots 1, 4[a]
Follett *et al.*, 1992[31]	37	Case series	4
Schultheiss *et al.*, 1992[56]	79	Case series	2, 4
Brazenor, 1987[22]	25	Case series	3, 4
Wagemans *et al.*, 1997[99]	10	Case series	3, 4
Lazorthes *et al.*, 1985[40]	52	Case series	1, 2, 5
Bloomfield *et al.*, 1995[20]	50	Case series	4, 5
Penn *et al.*, 1984[54]	12	Case series	4, 5
Penn and Paice, 1987[53]	43	Case series	4, 5
Winkelmuller and Winkelmuller, 1996[65]	120	Retrospective case series	4, 5

[a] *Choice of method depended on patient's condition. If patients had only a few weeks to live and preferred to stay at home they would have pump type 1. If hospitalised in the last weeks of life, single shots would be administered. Those with a type 4 pump had longer life expectancy and were fit enough to undergo surgery*

Cancer versus non-cancer pain

In five studies the use of intrathecal pumps in patients with non-malignant pain was specifically investigated (*Table 19a*). The authors of one other published study[28] evaluated intrathecal therapy on a mixed cancer/non-cancer group and concluded that it was not recommended for chronic non-malignant pain. Four of the five studies listed in *Table 19a* showed a generally positive effect of the therapy. Yoshida and colleagues did not recommend the use of intrathecal therapy in failed back surgery patients because the 'risks and sequelae of pump insertion far outweighed the benefits gained'.[67]

TABLE 19a *Intrathecal therapy for non-malignant pain*

Reference	No. patients	Outcome
Bloomfield *et al.*, 1995[20]	50	Benefit in 78%
Hassenbusch *et al.*, 1995[37]	18	Effectiveness was reported
Nitescu *et al.*, 1998[45]	90	Acceptable pain relief in 98%
Winkelmuller and Winkelmuller, 1996[65]	120	Effectiveness was reported
Yoshida *et al.*, 1996[67]	18	Not useful for the long-term management of non-malignant chronic pain

Risks

The risks of therapy have been divided into:

- pharmacological side-effects related to the drugs used (e.g. nausea and vomiting, respiratory depression, pruritus)
- mechanical complications of the pump systems (e.g. catheter occlusion, pump failure); also included in this section is meningitis.

Pharmacological side-effects

The incidence of side-effects from intrathecal therapy may appear to be high. However, the majority of this patient population have failed more conventional routes of opioid delivery. Furthermore, the magnitude of the side-effect impact on the individual is not obtainable from most of the literature. It should be recommended that anyone embarking on intrathecal therapy should be cognisant of the potential incidence of side-effects, particularly if this step is not at the end of the pain treatment continuum and if the use of systemic opioids has been suboptimal.

Further work is necessary to compare different opioid delivery routes. This should attempt to elucidate where the use of intrathecal opioids lies in the pharmacological strategies to minimise their attendant side-effects. For accurate comparisons to be achieved the validation of side-effects may be required. Although it is vital to be able to delineate the incidence of these, both for clinical practice and power investigations, they ultimately tell only one part of a complex multidimensional picture.

Problems with the data:

- Lack of comparator data. There are no comparator data assessing side-effects; all the information in this report is gathered from case

TABLE 20 *Details of different durations of intrathecal therapy*

Reference	No. patients	Patient type	Pump type	Follow-up period
Gestin *et al.*, 1997[33]	50	Cancer	1	7–584 days (mean 142)
Mercadante, 1994[43]	15	Cancer	1	Followed until death: 8–25 days (mean 15.7)
van Dongen *et al.*, 1993[61]	51	Cancer	1	90 days
Nitescu *et al.*, 1995[46]	200	Cancer	1	1–575 days (mean 33)
Nitescu *et al.*, 1998[45]	90	Non-cancer	1	Treatment 3–1706 days (median 60)
Sjoberg *et al.*, 1994[58]	53	Cancer	1	7–334 days (median 29)
Wagemans *et al.*, 1997[99]	10	Cancer	1	Mean duration of therapy 98 days (range 8–452)
Devulder *et al.*, 1994[30]	33	Cancer	2	Duration of treatment: < 22 days = 10 patients; 22–90 days = 11; > 90 days = 12
Parker *et al.*, 1987[51]	12	Cancer	2	0.5–28 months
Cheng *et al.*, 1993[24]	100	Cancer	2	12 weeks
Cobb *et al.*, 1984[25]	10	Cancer	2	4–254 days (mean 109)
Hardy and Wells, 1990[36]	8	Cancer	2	2 weeks
Madrid *et al.*, 1988[42]	100	Cancer	2	7 months
Sjoberg *et al.*, 1991[59]	52	Cancer	1,2	Continuous infusion: 4–255 days (median 22) All: 1–305 days (median 23)
Ventafridda *et al.*, 1987[62]	18	Cancer	1,2	1–231 days treatment (mean 46) 50% had catheter in at time of death
Follett *et al.*, 1992[31]	35 2	Cancer Non-cancer	4	44 months (mean 7.7) 1 patient followed up for 3.5 years
Coombs *et al.*, 1984[27]	6	Cancer	4	6 months[a]
Krames *et al.*, 1985[39]	11	Cancer Non-cancer	4	Mean 4.6 months
Muller *et al.*, 1988[44]	23	Cancer	4	203 days
Paice, 1986[50]	17	Cancer	4	Treatment time range: 1–31 months[b] (mean 7)
Shetter *et al.*, 1986[57]	9	Cancer	4	1–23 months (mean 5; median 3)
Wang, 1985[63]	62	Cancer	1,4	≥ 2 weeks pain relief considered successful
Anderson and Burchiel, 1999[19]	40	Cancer	5	24 months (assessments at 3, 6, 12, 18 and 24 months)
Chambers and MacSullivan, 1994[23]	12 3	Cancer Non-cancer	5	Until death or removal of pump owing to complications
Hassenbusch *et al.*, 1995[37]	18	Non-cancer	5	2.4 ± 0.3 years (range 0.8–4.7)[c]
Paice *et al.*, 1996[48]	140 289	Cancer Non-cancer	5	25 months
Tutak and Doleys, 1996[60]	26	Non-cancer	5	20–360 months (mean 115)[d,e]
Gourlay *et al.*, 1991[34]	10	Cancer	2,4	Continuous infusion: mean 169 days Bolus: mean 140 days[f]
Schultheiss *et al.*, 1992[56]	79	Cancer	2,4	Short-term survivors: 8 weeks Long-term survivors: 15 months
Lazorthes *et al.*, 1985[40]	52	Cancer	2,5	Mean 125 days

continued

TABLE 20 contd *Details of different durations of intrathecal therapy*

Reference	No. patients	Patient type	Pump type	Follow-up period
Brazenor, 1987[22]	23 3	Cancer Non-cancer	3,4	Average period for patients who died: 144 days Shortest survival: 12 days Non-cancer patients surviving, and 5/23 cancer patients
Bloomfield *et al.*, 1995[20]	50	Non-cancer	4,5	At least 4 months after implant surgery
Winkelmuller and Winkelmuller, 1996[65]	120	Non-cancer	4,5	0.5–5.7 years (mean 3.4)
Yoshida *et al.*, 1996[67]	18	Non-cancer	5	2 years[g]

[a] *Only 6 patients survived more than 6 months (epidural and intrathecal: patients had uniformly unsatisfactory responses after 6 months)*
[b] *It is assumed that treatment time was time until death.*
[c] *Patients seen at least monthly for 6 months; evaluations taken at these times*
[d] *This is the duration of pain; no other data specifying follow-up times*
[e] *Data collected by interviews at time of refill; forms completed by patients; telephone interviews; subjective rating*
[f] *Patients visited in home/hospice/hospital by research nurses, for psychometric tests; data not differentiated between epidural and intrathecal*
[g] *At end of follow-up: 8 pumps still in, 8 pumps removed, 2 lost to follow-up*

series studies. Single case studies have been excluded because they do not have a valid denominator (a valid sample from which side-effects and complications are presented).

- Problems with the denominator. The percentage incidence of side-effects will vary according to which figure is used as the denominator. For example, the incidence of pruritus is 10% of patients when all the studies are grouped together (the denominator number is large). However if only studies that specifically mention pruritis as a potential complication are used as the denominator (the denominator number is therefore smaller) then the incidence rises to 18%.
- Other problems with the data.
  - Side-effects are often reported in a binary fashion: present or not. In practice the severity of side-effects varies within an individual and between individuals.
  - The incidence of side-effects should be assessed in terms of duration of implantation in order to relate truly their impact on the individual. However this is often not reported.
  - Symptoms ascribable to pharmacological interventions may be attributable to disease progression or other causes, thus clouding the accuracy of reporting. The reverse of this is also true.
  - Reports of the use of combination drug therapies are relatively late and still evolving in the documented history of intrathecal therapy and thus their effect on overall side-effects may be seen to change with later reports.

Side-effects reported

The major side-effects are listed in *Table 21*.

TABLE 21 *Percentage reported incidence of side-effects*

Side-effect	% reported
Nausea and vomiting	25
Sedation	17
Urinary retention	19
Pruritus	17
Myoclonic activity	18
Respiratory depression	3

Other side-effects are:

- amenorrhoea
- altered libido
- constipation
- oedema
- opioid overdose
- polyarthralgia
- provocation of asthma
- parenteral abuse of opioids
- sweating
- incontinence.

Details of specific side-effects

Nausea and vomiting

- As with systemic opioids, nausea and vomiting is one of the most common side-effects of intrathecal therapy. In this analysis the overall incidence is 25% (*Table 22*).
- The extent and duration of nausea and vomiting are not discussed in many of the reports. Several authors suggested that the effects were predominantly transient.[24,65] This may be

TABLE 22 *Nausea and vomiting*

Reference	No. patients
Anderson and Burchiel, 1999[19]	8/40
Brazenor, 1987[22]	5/26
Cheng *et al.*, 1993[24]	40/100[a]
Follet *et al.*, 1992[31]	10/37
Madrid *et al.*, 1988[42]	9/100
Muller *et al.*, 1988[44]	5/23
Nitescu *et al.*, 1998[45]	18/90
Paice *et al.*, 1996[48]	108/429
Penn and Paice, 1987[53]	"Several"
Schultheiss *et al.*, 1992[56]	13/79
Tutak and Doleys, 1996[60]	3/26[b]
Ventafridda *et al.*, 1987[62]	21/53
Yoshida *et al.*, 1996[67]	3/18
Max *et al.*, 1985[86 c]	1/7[d]
Moulin *et al.*, 1985[88 c]	2/10
Nurchi, 1984[90 c]	1/9
Obbens *et al.*, 1987[91 c]	12/20
Total	272/1080 (25%)

[a] *Less than 1 week's duration*
[b] *Pain level at 12 weeks: 9% comfortable, 52% weak, 28% mild, 7% moderate, 4% severe*
[c] *Studies with bolus and/or intraventricular administration*
[d] *These data could not be included as it is unclear whether the patients were given morphine, methadone or a combination of the two drugs*

related to tolerance, dose adjustment or the introduction of co-medication. Cheng and colleagues[24] documented transient nausea and vomiting in 40% of patients in the first week, decreasing to 10% after 2 weeks. Winkelmuller and Winkel-muller[65] noted early nausea (36%) and vomiting (24%) in non-malignant pain patients. They did not regard it as a major problem in the long term.

- Some authors have documented a similar incidence of nausea with opioid/local anaesthetic compared with single-agent opioids.[45] A direct controlled study has yet to be reported.
- Nausea and vomiting may be related to the rostral spread of morphine. Brazenor[22] suggested that its incidence was increased with more cephalic positioning of the intrathecal catheter.
- Ventafridda and co-workers,[62] in a retrospective review of 412 patients, documented less nausea and vomiting when using the epidural route (18%) than the intrathecal (40%).
- The use of systemically administered breakthrough opioids may contribute to the overall incidence of nausea and vomiting. Several authors have reported systemic opioid use as varying from 15%[22] to 61%.[27] Anderson and Burchiel,[19] in their prospective study of 40 patients, documented that 30% were still on systemic opioids after 2 years of intrathecal therapy. Follet and co-authors[31] reported an incidence of 27% for nausea and vomiting, and acknowledged that in only four of the ten affected patients was it clearly attributable to intrathecal morphine.

Sedation and somnolence

The overall reported incidence of sedation and somnolence was 17%. Details are presented in *Table 23*.

- Sedation and somnolence have been reported as a problem with intrathecal as well as oral opioid medication. The nature, severity and duration of these side-effects and their impact on patients' quality of life are not frequently documented. The effects range from feelings of lethargy[19] to disorientation[83] and frank psychosis.[95] The advanced nature of this population's disease process will obviously have an impact on the incidence of central nervous system symptoms.

TABLE 23 *Sedation and somnolence*

Reference	No. patients
Anderson and Burchiel, 1999[19]	6/40[a]
Cheng *et al.*, 1993[24]	1/100[b]
Cobb *et al.*, 1984[25]	2/10
Follet *et al.*, 1992[31]	6/37
Muller *et al.*, 1988[44]	4/23
Ventafridda *et al.*, 1987[62]	27/53
Wang, 1985[63]	12/62[c]
Lenzi *et al.*, 1985[81 d]	4/38
Lobato *et al.*, 1983[83 d]	4/17
Max *et al.*, 1985[86 d]	2/7
Obbens *et al.*, 1987[91 d]	3/20
Total	71/407 (17%)

[a] *Anderson and Burchiel mention "lethargy"*
[b] *Longer than 2 weeks*
[c] *12 initial, 11 long term*
[d] *Studies with bolus or intraventricular administration*

- Various authors have reported incidences from 1%[24] to 51%.[62] The majority comment on the transient nature of these symptoms.
- The use of local anaesthetic would appear to reduce the incidence to 2–3%.[45,61]
- Spinal opioid switching has been reported to have some impact on somnolence. Krames and colleagues[78] noted that conversion from morphine to DADL restored analgesia, but sedation resumed on the reintroduction of morphine.

Urinary retention

The overall incidence of urinary retention was 18%. Data from individual studies are given in *Table 24*.

TABLE 24 *Urinary retention*

Reference	No. patients
Anderson and Burchiel, 1999[19]	1/40
Bloomfield *et al.*, 1995[20]	12/50
Brazenor, 1987[22]	2/26
Cheng *et al.*, 1993[24]	29/100
Follet *et al.*, 1992[31]	2/37
Hassenbusch *et al.*, 1995[37]	4/18[a]
Madrid *et al.*, 1988[42]	28/100
Meignier *et al.*, 1992[87]	5/5
Muller *et al.*, 1988[44]	10/23
Paice, 1986[50]	3/17
Parker *et al.*, 1987[51]	1/12
Penn *et al.*, 1984[54]	3/12
Schultheiss *et al.*, 1992[56]	5/79
Tutak and Doleys, 1996[60]	2/26[b]
Ventafridda *et al.*, 1987[62]	12/53
Wang, 1985[63]	15/62[c]
Yang *et al.*, 1996[66]	4/20
Lenzi *et al.*, 1985[81 d]	1/38
Lobato *et al.*, 1983[83 d]	1/17
Moulin *et al.*, 1985[88 d]	1/10
Total	141/745 (19%)

[a] *Partial*
[b] *Pain level at 12 weeks: 9% comfortable, 52% weak, 28% mild, 7% moderate, 4% severe*
[c] *Wang writes of "sphincter disorder". This figure will not be included in the final calculation as it is unclear whether this refers to constipation or urinary retention*
[d] *Studies with bolus or intraventricular administration*

- Urinary retention is a well-known side-effect of intrathecal opioids. The majority of these studies do not specify the severity of this problem, which can range from hesitancy to the requirement for long-term catheterisation.
- Early retention is seen as a particular problem with opioids,[45] in contrast with local anaesthetic and opioid combinations, where both early and late retention are encountered.
- Intraventricular and epidural opioids can cause urinary retention problems.[45,83] Muller and co-workers[44] reported an incidence of 43% with intrathecal opioids compared with 19–22% with epidural therapy.
- The local anaesthetic effect on detrusor and abdominal musculature, and the opioid effect on afferent input, can contribute to significant problems. The incidence of early retention (2–4 days) has been documented to be similar with opioids both alone or in combination with local anaesthetic drugs. Sjoberg and co-authors[59] reported an incidence of 27% (morphine median dose 8 mg and bupivacaine 7.5 mg/day), higher than the figures here for opioids alone, but consistent with combination intrathecal therapy. These authors also documented data supporting a dose–response curve for bupivacaine: one case of urinary retention in 23 patients receiving less than 30 mg of bupivacaine per day; two at greater than 60 mg; and three at doses greater than 100 mg. However Sjoberg and colleagues[98] commented that patients receiving intrathecal therapy often needed catheterisation for other reasons. Sphincteric incontinence, both urinary (3%) and faecal (1%), has been documented.[45]
- Anderson and Burchiel[19] reported an incidence of only 3% of urinary hesitancy and Cheng and co-workers[24] documented nearly 29% in the early stages, but this remained a problem in only 5%.

Pruritis

Data concerning the occurrence of pruritis are shown in *Table 25* (overall incidence 17%).

- Pruritis is considered by many as one of the most bothersome symptoms encountered with the use of intrathecal opioids. Fortunately it is often only transient.[48,84] Cheng and colleagues[24] reported an incidence of 36% during the first week and 0% after week 2 of intrathecal morphine therapy.
- In general, pruritus is uncommon in chronic administration of morphine.[48] The aetiology is thought to be of central origin. Its incidence is also well documented with the use of intraventricular (17%)[83] and epidural (27%)[62] routes.

TABLE 25 *Pruritus*

Reference	No. patients
Anderson and Burchiel, 1999[19]	6/40
Brazenor, 1987[22]	1/26
Cheng *et al.*, 1993[24]	36/100[a]
Madrid *et al.*, 1988[42 b]	13/100
Muller *et al.*, 1988[44]	6/23
Paice, 1986[50]	"Occasional" [c]
Paice *et al.*, 1996[48]	57/429
Tutak and Doleys, 1996[60]	4/26[d]
Wang, 1985[63]	14/62
Yang *et al.*, 1996[66]	5/20
Nurchi, 1984[90 e]	1/9
Total	143/835 (17%)

[a] *Duration < 1 week*
[b] *This table does not include Madrid, 1987, as it is assumed that these are the same 35 patients*
[c] *These data are not used in the cumulative calculation*
[d] *Tutak and Doleys state that these causes are "possibly" due to the use of morphine; fentanyl was also used in the study*
[e] *Study with "single-shot" (bolus) and/or intraventricular administration*

- The severity of the pruritis may vary from major discomfort or pain to tolerable symptoms. The average incidence from this series was 17%. This figure falls within the range of some of the individual reports,[70,92] although some have documented pruritus in up to 39%.[62,98] The introduction of a local anaesthetic may limit the incidence. Nitescu and co-workers,[45] in a report on 90 long-term externalised pumps for non-malignant pain, documented only one case of pruritus, although it must be noted that they used relatively small quantities of intrathecal morphine (1.4–25 mg equivalents/day) compared with others.

Myoclonic activity:

- Myoclonic activity is a known complication of opioid therapy, irrespective of its route. Its occurrence has been documented after oral, epidural and intraventricular therapy.
- Spasms may occur with centroaxial therapy, at relatively modest opioid doses (30 mg morphine) compared with previously used oral doses (3 g).[68] Its relatively recent association with opioid therapy may perhaps explain the low incidence of reporting and the reason for it being noted as an incidental event in only one study. It has been documented to occur not only with intrathecal morphine boluses[75] and infusions,[72] but with diamorphine,[68] sufentanil[73] and hydromorphone.[94]
- Krames and colleagues[39] reported two of 17 patients with spasm while receiving morphine 21.4 mg/24 h and 37 mg/24 h, which was controlled with oral baclofen and disappeared on withdrawal of the morphine. Both had evidence of metastatic disease in the vertebral column. Some authors have reported myoclonic spasm in patients with complete spinal block.[68] The aetiology is suggested to be an antiglycinergic effect at spinal level or the effect of morphine and its metabolites on post-synaptic inhibition.[74] Successful control has been achieved with oral baclofen and parental midazolam[82] before opioid withdrawal becomes necessary. Spinal opioid rotation is, unfortunately, not always the answer.[68]

Respiratory depression

From the studies cited in *Table 26*, the overall incidence of respiratory depression is 3%.

- Respiratory depression in people who are already tolerant to opioids has previously been considered to be extremely rare. The extent of respiratory depression is not always documented. It covers the spectrum of transient hypoventilation to complete cessation of respiratory activity.
- Some non-users of intrathecal therapy have cited the risk of respiratory depression as the key reason for not introducing intrathecal pump systems into their repertoire of interventions (telephone survey, chapter 7).
- Many studies, both prospective[19] and retrospective,[33,59] make little reference to its occurrence. Ventafridda and co-workers[62] documented a frequency of 2% with intrathecal therapy and 0% with epidural therapy.
- Respiratory depression has been documented during intraventricular opioid use.[83] Krantz and Christensen[79] reported accidental intrathecal placement with an epidural system. This led to hypopnoea 4 hours after a dose of morphine.

Local anaesthetic side-effects:

- In general, these are not reported with such clarity as the side-effects associated with opioids, many of which appear to be greatly reduced by the introduction of local anaesthetic. The side-effects commonly reported to be associated with local anaesthetics are: urinary retention, paraesthesia, paresis and orthostatic impairment.
- From the analysis of these reports, 20% were affected with paraesthesia. Sjoberg and co-

TABLE 26 *Respiratory depression*

Reference	No. patients
Coombs *et al.*, 1984[27] [a]	1/6
Lazorthes *et al.*, 1985[40]	3/52
Parker *et al.*, 1987[51]	1/12[b]
Madrid *et al.*, 1988[42]	1/100
Nitescu *et al.*, 1998[45]	1/90
Ventafridda *et al.*, 1987[62]	1/53
Lazorthes *et al.*, 1985[40] [c]	1/18
Lenzi *et al.*, 1985[81] [c]	1/38
Lobato *et al.*, 1983[83] [c]	1/17
Nurchi, 1984[90] [c]	1/9
Total	12/395 (3%)

[a] *Although it was not possible to include data on side-effects from Coombs* et al., *1984*[27] *because intrathecal and epidural data were combined, the one instance of respiratory depression was indicated as occurring in an intrathecal patient*
[b] *This was reported as one case of apnoea*
[c] *Studies with bolus or intraventricular administration*

workers[58] documented no paresis with doses of bupivacaine < 45 mg/day and an incidence of 9/27 at > 45 mg/day. They also showed evidence to suggest a dose–response for the development of urinary retention with bupivacaine.
- With low levels of local anaesthetic there are fewer side-effects. With higher levels (> 60 mg/day) only 50% of patients were reported by Nitescu and colleagues[89] to experience side-effects related to the local anaesthetic. This group has also documented 33% transient paraesthesia, 22% transient paresis and 10% arterial hypotension.

Other side-effects

Numerous other side-effects have been reported to be associated with intrathecal opioids.

- The most common is constipation, with reports of 20–30%,[19,24,65] but it has been noted to be as high as 50%. An overlap with systemic therapy could be significant, so the timing of these side-effects should be noted. Cheng and co-workers[24] documented its transient nature and reported, like others,[44] long-term problems in less than 5% of patients.
- Altered sexual function has also been documented.[23,49,65]
- Amenorrhoea and polyarthralgia have been reported[23,69] and also reduced libido.[48,49] Paice and co-workers[49] reported that four of six men who were receiving intrathecal morphine or hydromorphone (mean dose 18.5 mg morphine equivalent) had problems with impotence and reduced testosterone levels within 1 month of commencing therapy. Winkelmuller and Winkelmuller[65] commented that the majority of these symptoms disappeared by 14 months. The expectation that long-term implantation would lead to altered body image and to individual and family emotional problems is not well documented. In fact, Cobb and colleagues,[25] in a series of patients receiving intrathecal opioids for pelvic and sacral pain, noted that the help required with the administration of this therapy actually brought partners closer.
- Overdose and abuse have been documented. A bolus dose of morphine 450 mg was reported to result in hypertension, status epilepticus, respiratory problems and intraventricular haemorrhage.[97] Wu and Patt[101] reported an accidental subcutaneous injection (18 ml of 25 mg/ml morphine) with a Synchromed pump. The patient recovered uneventfully and remained on intrathecal therapy. Cherry and Eldridge[70] reported a case of morphine abuse with a Synchromed pump. They documented that a patient undertook deliberate withdrawal of the reservoir contents and subsequent parental administration. Yoshida and colleagues[67] noted one case of oral opioid substance abuse in a series of 18 patients with non-malignant pain.
- Sweating and peripheral oedema have been documented by several authors.[62,65] The incidence of sweating is often not noted and has been variably reported from 8.5%[65] to 41%.[62] Oedema has also been consistently reported in the literature.[48,62,65] Paice and co-workers[48] noted a 12% incidence with intrathecal morphine.
- Winkelmuller and Winkelmuller[65] suggested that intrathecal opioids were responsible for the provocation of asthma in one patient in their series of 120.

Mechanical complications

Intrathecal therapy's encouraging results are tempered by the complication rates. The attendant physical and technical problems associated with the mechanical delivery systems for this treatment will have obvious implications on the overall outcome of intrathecal opioid therapy.

All systems used are prone to complications, irrespective of whether they are simple percutaneous catheters or fully implanted devices. The highest incidence of problems is attributable

to the catheter. The extent and impact on the individual patient and the pecuniary toll will be dependent on the complexity of the necessary reparations. Type 5 pump systems undergo less dislodgement than type 1 systems, but the efforts to effect the restoration of analgesia will be much greater. Ultimately, the extent to which these facts are tolerated by the patient, the clinician and purchasers will depend on the clinical scenario and local amenities. Future reporting should attempt to analyse different systems concomitantly and detail related complications on a temporal basis.

Problems with the data:

- Different types of device: There are no direct comparisons between different types of intrathecal device. The majority of those reported are either type 1 or type 5 pumps. These are at the opposite ends of the spectrum of available technology and they are usually used in different patient populations.
- Different durations of pump implantation: The length of time a catheter system is *in situ* will impact on issues of effectiveness and complications. Only a few groups have reported on complications that are based on duration. For many studies it is not possible truly to delineate this relationship. However, this is necessary if comparisons of low-technology and more expensive fully implantable devices are to be made.
- Different disease types: The attributable complications of the different types of device will vary depending on the technology and the pathology. The level to which these are tolerated will vary according to the clinical scenario.

Potential complications

Meningitis

Table 27 lists studies that recorded the numbers of patients who developed meningitis after intrathecal pump implantation. The data are arranged according to the type of intrathecal pump device used.

- Overall incidence: Fourteen meningitis cases were reported in a total of 454 patients (3%). There were no deaths related to catheter-associated meningitis. The majority of patients were treated conservatively, allowing the system to remain *in situ*, with continuation of therapy.
- Duration of pump implantation: Some of the studies cited in *Table 28* give an indication of the duration of pump implantation prior to the development of meningitis.
- Intrathecal versus epidural administration: Epidural placement has been suggested to reduce the incidence of meningitis,[39] but infection rates have been shown to be similar.[46]
- Meningism versus meningitis: Although some studies differentiated aseptic meningism from meningitis, the diagnostic criteria were not always clear. Groups reporting meningitis have occasionally not been able to trace an organism.[71]

Catheter-related complications

Catheter-related problems are often seen as the main complication of these systems.[48]

TABLE 27 *Meningitis*

Reference	Intrathecal pump type					Intraventricular delivery	Drugs used
	1	2	3	4	5		
Cheng *et al.*, 1993[24]		1/100					Morphine
Devulder *et al.*, 1994[30]	3/33[a]						Morphine[b]
Lazorthes *et al.*, 1985[40]					1/52		Morphine
Nitescu *et al.*, 1995[46]	1/200						Morphine + bupivacaine
Parker *et al.*, 1987[51]		1/12[c]					Morphine
Schoeffler *et al.*, 1986[55]				6/37			Morphine
Obbens *et al.*, 1987[91 d]						1/20	Morphine
Total (14/454)	4/233	2/112	0	6/37	1/52	1/20	

[a] *Devulder* et al., *1994[30] stated that "this could be attributed to accidental disconnections in the external tubing of the pump system" (p. 77)*
[b] *Morphine and/or clonidine, calcitonin, bupivacaine*
[c] *Also one case of pseudomeningocoele*
[d] *Study with bolus or intraventricular administration*

TABLE 28 *Onset of meningitis after catheter insertion*

Reference	Days after catheter insertion
Cheng *et al.*, 1993[24]	> 14
Obbens *et al.*, 1987[91]	21
Parker *et al.*, 1987[51]	662
Schoeffler *et al.*, 1986[55]	8–100

There were problems with the data:

- The terminology reported in the different series is not standardised; thus, disconnection from the reservoir hub may be documented as dislodgement in one series and not in another.
- Many authors combine these complication, as in the case series reported by Ventafridda and co-workers,[62] who documented a 47% incidence of side-effects or dislodgement in type 1 systems within the first month. Some studies report considerably lower incidences.[24,42]
- The duration of pump implantation may affect the incidence of complications.

Catheter dislodgement. *Table 29* lists the reported incidence of catheter dislodgement. Combining all the data, the overall incidence is between 5% and 18%. Many studies did not describe this complication and it is often not clear whether this means that it did not occur or whether it was just not reported.

- The overall incidence reflects a more frequent occurrence of dislodgement of type 4 pumps (18%) and type 5 (13%) compared with 5% for type 2 systems.

Catheter collapsing/kinking. The numbers of reported cases of catheter kinking are presented in *Table 30*.

Obstruction or occlusion. The documented incidences of catheter obstruction or occlusion are shown in *Table 31*. Catheter occlusion can occur for a number of reasons:

- Tutak and Doleys[60] reported on a series of type 5 systems and noted that the catheters lost elasticity and suffered luminal closure under pressure.
- Cheng and colleagues,[24] in a series of type 2 systems, noted that two out 100 were obstructed secondary to an anterior chest wall haematoma, and that the overall incidence of obstruction after 2 weeks was 5%.
- The diagnostic use of radiopaque dye or CSF aspiration[20] has proved useful in elucidating catheter-related problems.

TABLE 29 *Intrathecal pump catheter dislodgement*

Reference	Intrathecal pump type				
	1	2	3	4	5
Anderson and Burchiel, 1999[19]					2/30
Bloomfield *et al.*, 1995[20]				7/50	
Chambers and MacSullivan, 1994[23]					1/15
Cheng *et al.*, 1993[24]		2/100			
Coombs *et al.*, 1984[27]				2/6	
Devulder *et al.*, 1994[30]		4/33			
Gestin *et al.*, 1997[33]		2/40			
Hassenbusch *et al.*, 1995[37]					5/18
Krames *et al.*, 1985[39]				3/11	
Mercadante, 1994[43]	1/15				
Muller *et al.*, 1988[44]				1/23	
Nitescu *et al.*, 1995[46]	11/200				
Paice, 1986[50]				2/17	
Penn *et al.*, 1984[54]				2/5	
van Dongen *et al.*, 1993[61]	13/51				
Winkelmuller and Winkelmuller, 1996[65]				25/119	
Total (%)	9	5	0	18	13

TABLE 30 *Number of cases of catheter kinking*

Reference	Intrathecal pump type		Drugs used
	4	5	
Bloomfield *et al.*, 1995[20]	2/50		Morphine
Chambers and MacSullivan, 1994[23]		1/15	Morphine
Hassenbusch *et al.*, 1995[37]		2/18	Morphine + sufentanil
Penn and Paice, 1987[53]	"Several"		Morphine
Yoshida *et al.*, 1996[67]	7/18		Morphine

- Fibrous encapsulation is not as big a problem in the subarachnoid space as it is in the epidural space. However, intrathecal scar tissue[20] may necessitate epidural or systemic drug delivery. Some have resorted to intermittent bolus injection to overcome such problems.[30]

TABLE 31 *Catheter closure/occlusion or disconnection*

Reference	Intrathecal pump type				
	1	2	3	4	5
Bloomfield *et al.*, 1995[20]					11/50[a]
Chambers and MacSullivan, 1994[23]					1/15
Madrid *et al.*, 1988[42]		8/100			
Nitescu *et al.*, 1995[46]	3/200				
Tutak and Doleys, 1996[60]					7/26
Shetter *et al.*, 1986[57]		2/6			
van Dongen *et al.*, 1993[61]	9/51				
Brazenor, 1987[22]		4/19			
Cheng *et al.*, 1993[24]		2/100			
Gestin *et al.*, 1997[33]		5/100			
Krames *et al.*, 1985[39]				4/17	
Muller *et al.*, 1988[44]				1/23	
Anderson and Burchiel, 1999[19]					1/30
Total 45/587 (%)	12/251 (5)	19/225 (8)	0	5/40 (13)	9/71 (13)

[a] *Data not included in table totals*

TABLE 32 *Mechanical/pump failure using type 5 intrathecal pump*

Reference	No. patients reporting type 5 pump failure	Drugs used
Anderson and Burchiel, 1999[19]	7/40[a]	Morphine
Chambers and MacSullivan, 1994[23]	1/15	Morphine
Hassenbusch *et al.*, 1995[37]	1/18	Morphine + sufentanil
Paice *et al.*, 1996[48]	82/380[b]	Morphine
Paice *et al.*, 1996[93]	1/2	Morphine + octreotide
Penn *et al.*, 1984[54]	2/12[c]	
Penn and Paice, 1987[53]	4/19[d]	Morphine
Total	98/486	

[a] *Mechanical dysfunction = 5, pump malfunction = 2*
[b] *Delivery system complications*
[c] *4 failed but 2 of these were due to leakage and are included in Table 33*
[d] *Problems with pumps were overcome in a newer model*

Catheter migration.

- Migration of the catheter from the subarachnoid space to the subdural space[31] and to the epidural space[99] has been documented.
- Wagemans and co-workers,[99] reporting on the neurohistopathological findings in ten patients, demonstrated that, when the catheter's position could be determined, in all cases it had migrated (one epidurally, two cranially, and five caudally).

Pump mechanical failure

- The incidence of mechanical failure amongst type 5 pumps is high. According to the data in *Table 32*, 20% of these pumps fail.
- In one case,[67] malfunction of an infusion device resulted in the spontaneous discharge of the reservoir's contents (morphine) into the patient.
- As reported by Hassenbusch and colleagues,[37] cases of rotor stall (1/18) and battery failure (7/18) are more common.
- One group noted leaking pumps leading to erosion of the electronic circuitry.[48]

CSF leakage

Some authors see CSF leakage as the most common complication. The data presented in *Table 33* indicate an incidence of 10%.

- The technique of feeding a catheter through a trocar will lead to a larger window in the dura; thus, some degree of CSF loss is seen as inevitable.[92] This may result in an observed loss of fluid or a fluid collection.[51]
- A paramedian approach to the dura has been advocated[33] to reduce the incidence of leakage and post-dural puncture headache.
- A variety of manoeuvres, from conservative treatment and an epidural blood patch[46] to fibrin glue,[32,65] have been employed to provide biological seals. Ultimately, surgical revision may be necessary to repair the dural tear.

Haematoma/seroma/fistula

The occurrence of seromas is thought to be inconsequential unless they become infected.[48] In such cases they provide a direct conduit to the CSF. The size is related to the size of pocket fashioned, the elasticity of adjacent tissue, and surgical wound healing. However they usually resolve within 1 to 2 weeks.[48] The incidences reported in type 4 pumps are given in *Table 34*.

TABLE 33 *CSF leakage*

Reference	Intrathecal pump type					Single bolus	Intra-ventricular	Drugs used
	1	2	3	4	5			
Cobb *et al.*, 1984[25]		2/10[a]						Morphine
Devulder *et al.*, 1994[30]	3/33							Morphine[b]
Gestin *et al.*, 1997[33]	6/50							Morphine
Jin *et al.*, 1986[38]				1/2				ß-Endorphin
Nitescu *et al.*, 1998[45]								Morphine + bupivacaine
Penn *et al.*, 1984[54]					2/12			Morphine
Schultheiss *et al.*, 1992[56]						1/79		Morphine
van Dongen *et al.*, 1993[61]	3/51							Morphine + bupivacaine
Wang, 1985[63]	6/28[c]							Morphine
Yoshida *et al.*, 1996[67]					3/18			Morphine
Gerritse *et al.*, 1997[32 d]						3/3		Morphine + bupivacaine
Obbens *et al.*, 1987[91 d]							1/20	Morphine
Parker *et al.*, 1987[51 d]		1/12						Morphine
Total 32/318	18/162	3/22	0	1/2	5/30	4/82	1/20	

[a] *Also CSF fluid around reservoir*
[b] *Morphine and/or clonidine, calcitonin, bupivacaine*
[c] *This concerns long-term use*
[d] *Studies with bolus or intraventricular administration*

TABLE 34 *Haematoma/seroma (type 4 pump)*

Reference	Intrathecal pump type 4	Drug used
Coombs *et al.*, 1984[27]	1/6	Morphine
Follet *et al.*, 1992[31]	2/37[a]	Morphine
Schultheiss *et al.*, 1992[56]	4/79[b]	Morphine
Total	7/122	

[a] *Seroma*
[b] *At thoracic site; unclear whether the seroma was with type 2 or type 4 pump*

TABLE 35 *Fistula*

Reference	Intrathecal pump type			Drug used
	2	4	5	
Chambers and MacSullivan, 1994[23]			1/15	Morphine
Coombs *et al.*, 1984[27]		2/6		Morphine
Madrid *et al.*, 1988[42]	4/100			Morphine
Shetter *et al.*, 1986[57]		1/9		Morphine
Total 8/130	4/100	3/15	1/15	

Fistulas may also occur, however these have been noted to close spontaneously.[42] *Table 35* shows the reported incidences in pump types 2, 4 and 5.

Selecting patients for intrathecal therapy

Indications for the use of intrathecal pump systems

Intractable pain

Forty eight out of 77 studies (62%) included a statement that intrathecal therapy was used only in patients with intractable pain that was resistant to conventional analgesic delivery. A variety of statements were used to describe the level and severity of pain that needs to be experienced prior to consideration for administration of this therapy:

- pain refractory to conventional measures[25]
- pain unrelieved by other methods[40]
- pain totally dominating life[45]
- inability to treat pain successfully[65]
- inadequate pain relief[61]
- inability to control pain in other ways.[24]

The authors of a number of articles wrote generically of other techniques and routes being tried and found to be ineffective.[31,33,37,45,50,58,60,61,65,80]

Many noted the problems with escalating or ineffectual oral or parenteral narcotics.[23,31,43,44,53,56,59,63] Some specified the failure of neuro-ablative or neurosurgical procedures.[33,50,53,54] Others examined the problems caused by the failure of systemic and co-analgesics/other adjuvant drugs.[30,34] Ventafridda and colleagues[62] discussed inefficacy caused by intolerance to opioids.

Side-effects from conventional routes of analgesia delivery

It was mentioned in many studies that pain was relieved by conventional analgesics until unacceptable or intolerable side-effects prevented the continuation of systemic therapy. Problems with side-effects associated with systemic narcotics were mentioned by many authors.[22,44,45,50,53,59,63,65]

Other issues relating to the selection of patients for intrathecal therapy

Life expectancy

Life expectancy for cancer patients is usually shorter than for non-cancer patients. The implications of this would be relevant when assessing issues of cost and benefit. The cost–benefits of intrathecal opioid therapy for patients with a short expected life span may not be realised, although the benefits in terms of quality of life may provide a strong argument for its use. In the telephone survey reported in chapter 7, there were some strong opinions on this matter, with practitioners suggesting that this therapy was suitable only for cancer patients or, conversely, only for non-cancer patients.

In the published reports, Ventafridda and co-workers[62] suggested that it is useful for chronic cancer patients, while Lipman and Blumenkopf[41] stated its appropriateness for pain in metastatic cancer. Muller and colleagues[44] agreed that "intrathecal opioids in benign pain cannot be advocated in general, as our long term experience is still very limited".

Table 36 shows the range of opinion concerning life expectancy and cancer patients. It can be seen that the range is relatively far reaching and covers anything from about 2 weeks to over 6 months. Only Penn and co-workers[54] wrote in terms of years rather than months.

The use of pumps in non-cancer patients

Since 1988 there has arisen an extensive literature on the use of intrathecal pumps in non-cancer pain patients. In particular, Krames[77] has described the use of long-term spinal (intrathecal and epidural) opioid delivery. He mentions that it is particularly important in non-malignant patients to consider the use of intrathecal pumps only at the end of a long treatment continuum when all alternative therapies have been tried (i.e. as a treatment of last resort).

The treatment continuum for non-malignant pain, as set out by Krames,[77] is as follows:

- over-the-counter drugs
- NSAIDs
- muscle relaxants
- physical and occupational therapies
- rehabilitation medicine
- cognitive–behavioural therapies
- nerve blocks
- surgery
- weak opioids
- strong opioids
- spinal cord stimulation
- intraspinally administered opioids
- destructive neuroablative procedures.

In this group of patients the use of intrathecal pumps is controversial also because the utilisation of systemic opioids is not well established in non-malignant pain.

Types of pain

Two principle types of pain exist: neuropathic and nociceptive. Traditionally, nociceptive pain has been considered to be opioid sensitive and neuropathic pain opioid resistant.

- Hassenbusch and colleagues[37] considered that this therapy is appropriate only for neuropathic pain, while Gestin and co-workers[33] suggested

TABLE 36 *Life expectancy as an inclusion criterion for using intrathecal pumps in cancer patients*

Reference	Life expectancy
Wang, 1985[63]	≥ 2 weeks
Obbens *et al.*, 1987[91]	> 1 month
Mercadante, 1994[43]	< 2 months
Brazenor, 1987[22]	> 2 months
Chambers and MacSullivan, 1994[23]	> 3 months
Follett *et al.*, 1992[31]	> 3 months
Cheng *et al.*, 1993[24]	> 3 months
Coombs *et al.*, 1984[27]	≥ 4 months
Muller *et al.*, 1988[44]	> 6 months
Penn and Paice, 1987[53]	> Few months
Penn *et al.*, 1984[54]	Several months to years

that it should be used for nociceptive or mixed nociceptive–neuropathic pain.
- Paice[50] considered the therapy suitable for patients who do not have pain at or above the mid-cervical dermatome. This was reinforced by Penn and colleagues.[54] Wang[63] suggested it should be used when the pain is limited to the pelvic or perineal area, or to the lower extremities, and to patients with no neurological or sphincter disturbance.
- Sjoberg and co-workers[58] specified the type of pain as that which has previously been shown to be inadequately treated by epidural local anaesthetics and/or opioids or intrathecal opioids.
- Tutak and Doleys[60] suggested that there should be no surgical lesion that has been judged to be a cause of the pain, and Brazenor[22] advised ensuring that there are no actual or impending blockages of the subarachnoid space.
- Cheng and colleagues[24] advised against utilising this therapy for head and neck pain.

Exclusion criteria

There are some reported specific indications of when patients should be excluded from this therapy:

- when there is a significant psychiatric disorder, a personality disorder, an addictive personality, or a mental or true allergy to morphine or sufentanil[37]
- in depression, senility, suspected pain behaviour or malingering, alcohol or opioid abuse, and associated severe physical conditions[45]
- in psychiatric illness.[65]

Home and community factors

The physiological indications for the successful use of this therapy may exist apart from environmental factors, which, while being of a secondary nature as inclusion criteria, are nevertheless valid. They include:

- the presence of a favourable environment for ambulatory surveillance[40]
- intact family function[24] for family members to be able to administer the therapy at home.[91]

Trial of intrathecal opioid therapy prior to pump implantation

Published studies concerned with intrathecal trials of spinal opioids prior to pump implantation are detailed in *Table 37*.

- Before a patient is considered for intrathecal therapy, Anderson and Burchiel,[19] Coombs and colleagues,[27] Krames and co-workers[39] and Follett and co-authors[31] all suggested that there should be at least a 50% decrease in baseline pain after a trial of spinal opioid (either epidural or intrathecal).
- Follett's group[31] reported that the pain relief should last for at least 12–16 hours, but, if unsuccessful, these patients should be given a second chance the next day by administering a double dose of opioids.
- Madrid and colleagues[42] noted simply an "effective" test dose, and Obbens and co-workers[91] indicated that there should be "adequate pain relief for several hours". Wang[63] suggested that patients should be excluded if they have not achieved pain relief with 2 mg of morphine or if they have intolerable side-effects.
- Paice[50] considered the place of systemic narcotics during screening and proposed that they should be reduced by 50% prior to a successful trial being claimed.
- Tutak and Doleys[60] drew attention to the beneficial effects of objective assessment and recommended the services of a behavioural psychologist after an intrathecal trial.

Types of trials. Four types of trials are reflected in the studies: intrathecal bolus or infusion, and epidural bolus or infusion. The numbers of patients reported (in *Table 37*) as undertaking the various tests are shown in *Table 38*.

Other inclusion criteria. Some authors did not utilise a neuraxial opioid trial prior to commencing intrathecal therapy (*Table 39*); instead, they used other inclusion criteria to determine patient suitability.

TABLE 37 *Details of studies using initial intrathecal trials of spinal opioids prior to pump implantation*

Reference	No. patients	Patient type	Type of trial	Drug used	Dosage	Criteria for inclusion	Notes
Anderson and Burchiel, 1999[19]	40	Cancer	Intrathecal bolus (14/40) Epidural pump and temporary catheter: 2–3 days (26/40)	Morphine	1 mg	Neurological and neuropsychological assessments Intrathecal bolus: pain relief of at least 50% Epidural infusion: pain relief of at least 50%	
Bloomfield *et al.*, 1995[20]	50	Non-cancer	Intrathecal	Morphine bolus injection			Implanted if experienced adequate pain relief and avoided significant side-effects
Chambers and MacSullivan, 1994[23]	15	12 Cancer 3 Non-cancer	Epidural	Morphine	Increased 12-hourly intervals Screening lasted 4–7 days	Life expectancy > 3 months No pain relief despite escalating doses of strong narcotics Intolerable side-effects	
Cobb *et al.*, 1984[25]	10	Cancer	Single lumbar puncture injection	Morphine	1–2 mg	Refractory to conventional measures	7/10 were injected
Coombs *et al.*, 1984[27]	6	Cancer	Epidural	Morphine		50% decrease in baseline pain Expected survival ≥ 4 months	
Follett *et al.*, 1992[31]	37	35 Cancer 2 Non-cancer	Intrathecal injection 24 h	Morphine	1/10 total daily narcotic intake, adjusted according to patient weight: 1–4 mg Test dose not exceeding 8 mg	Inability to control pain with oral narcotics or intolerance to their side-effects Life expectancy > 3 months Inappropriateness of other procedures	Suitable if trial gave > 50% reduction in pain for at least 12–16 h Patient given 2nd chance next day with double dose
Gourlay *et al.*, 1991[34]	10	Cancer	Epidural bolus or infusion over 2 days	Morphine		"Optimised" oral therapy with opioids and other adjuvant drugs could no longer provide effective analgesia	
Hassenbusch *et al.*, 1995[37]	18	Non-cancer	Intrathecal infusion 2–5 days	Morphine	Morphine or sufentanil Morphine 0.05 mg/h Sufentanil 0.05 µg/h Increased dose every 12 h with no side-effects or at morphine 2 mg, sufentanil 2 µg	Only neuropathic pain and no other treatment options ≤ 25% pain reduction with oral opioids and no intolerable side-effects (Excluded if significant psychiatric disorder, personality disorder, addictive personality, mental or true allergy to morphine or sufentanil)	Monitored sleep, appetite, supplemental systemic opioid use, and activity level during screening Sufentanil chosen as first drug but changed to morphine if not sufficient pain relief 4/18 did not obtain sufficient pain relief initially

continued

TABLE 37 contd *Details of studies using initial intrathecal trials of spinal opioids prior to pump implantation*

Reference	No. patients	Patient type	Type of trial	Drug used	Dosage	Criteria for inclusion	Notes
Krames *et al.*, 1985[39]	17	16 Cancer 1 Non-cancer	Single intrathecal bolus	Morphine	1–2.5 mg Mean 1.65 mg	≥ 50% pain relief from trial	
Lazorthes *et al.*, 1985[40]	52	Cancer	Intrathecal injection	Morphine	1–3 mg	Pain unrelieved by other methods Bilateral, mid-line or diffuse pain Presence of favourable environment for ambulatory surveillance	
Lipman and Blumenkopf, 1989[41]	5	Cancer	Intrathecal lumbar catheter	Morphine	1 mg	Suffered pain of metastatic cancer	
Leavens *et al.*, 1982[80]	6	Cancer	Bolus, subarachnoid space or frontal region	Morphine[a]	0.5 mg 1 mg	Unsatisfactory pain relief with other methods	0.5 mg gave relief for 12–14 h 1 mg gave relief for 10–25 h
Lobato *et al.*, 1983[83]	17	Cancer	Bolus[b]	Morphine[a]	0.5–0.75 mg	Unsatisfactory pain relief with other methods	0.5 mg gave relief for 12–14 h 1 mg gave relief for 10–25 h
Madrid *et al.*, 1988[42]	100	Cancer	Single intrathecal bolus	Morphine	0.5 mg	Test dose effective and did not result in side-effects	
Mercadante, 1994[43]	15	Cancer	Intrathecal	Morphine (no bupivacaine given at this stage)	1 mg	Life expectancy < 2 months Initial Karnofsky performance status ≥ 30 Oral or parenteral morphine could not provide satisfactory pain relief	Unclear whether this was a trial or not Bupivacaine added only once treatment was under way No outcomes of trial given
Nitescu *et al.*, 1998[45]	90	Non-cancer	Intrathecal injection	Bupivacaine	2.5–15 mg (median 8)	Pain dominated life totally Failure of other methods Unacceptable side-effects Depression, senility, suspected pain behaviour and malingering, alcohol/opioid abuse, and associated severe physical conditions were **not** contraindications	Excellent list of pain relief and doses according to type of pain

continued

TABLE 37 contd *Details of studies using initial intrathecal trials of spinal opioids prior to pump implantation*

Reference	No. patients	Patient type	Type of trial	Drug used	Dosage	Criteria for inclusion	Notes
Obbens *et al.*, 1987[91]	20	Cancer	Lumbar intrathecal	Morphine	1/100th i.m. dose (up to max. 16 mg)	Life expectancy > 1 month Family members to administer at home Adequate pain relief for several hours	
Paice, 1986[50]	17	Cancer	Epidural 2–3 days	Morphine		No pain relief from other routes Major side-effects from systemic narcotics Pain not relieved by ablative neurosurgery Patients who do **not** have pain at or above the mid-cervical dermatome	2–3-day trial had to achieve 50% reduction in systemic narcotics during screening to be included in its administration
Paice *et al.*, 1996[48]	429[c]	Cancer (32.7%) Non-cancer (67.3%)	Epidural infusion 151 patients Intrathecal injection 145 patients Epidural injection 105 patients Intrathecal infusion 28 patients				Screening blinded with saline performed in 18.3%
Penn *et al.*, 1984[54]	12	Cancer	Epidural infusion	Morphine	4.8 mg/day Increased to 14.4 mg/day	Life expectancy several months to years Location below mid-cervical dermatomes Inappropriateness of standard neurosurgical procedures for pain relief	
Penn and Paice, 1987[53]	43	35 Cancer 8 Non-cancer	Epidural Test lasted up to 5 days	Morphine	0.1 mg increase in dose at 12 and 24 h	Life expectancy > few months Inability to control pain with oral narcotics or intolerance to their side-effects Location below mid-cervical dermatomes Inappropriateness of neurosurgical procedures for pain relief	

continued

TABLE 37 contd *Details of studies using initial intrathecal trials of spinal opioids prior to pump implantation*

Reference	No. patients	Patient type	Type of trial	Drug used	Dosage	Criteria for inclusion	Notes
Shetter *et al.*, 1986[57]	24	Cancer	Epidural	Morphine	Bolus, 2–6 days (median 4) 5 mg/12 h (range 3.75–7.5 mg/6–24 h)	Subjective evaluation Supplemental narcotic requirements More pain relief than other routes and no side-effects 14/24 regarded as successful	
Sjoberg *et al.*, 1991[59]	52	Cancer	Intrathecal 48–72 h	Morphine + bupivacaine	Morphine 1–6 mg Bupivacaine 1–12.5 mg	Inability to control pain with oral narcotics or intolerance to their side-effects	Duration of analgesia in test served as basis for rest of daily doses
Sjoberg *et al.*, 1994[58]	53	Cancer	?	Morphine + bupivacaine	Morphine 0.25 mg Bupivacaine 0.2.25–7.5 mg	Pain resistant to other routes and methods Type of pain previously shown to be inadequately treated by epidural local anaesthetics and/or opioids or intrathecal opioids	
Tutak and Doleys, 1996[60]	26	Non-cancer	Epidural steroid injections – if no pain relief, single injection of morphine	Morphine	1–3 mg	Inadequate pain relief via more conservative measures Absence of surgical lesion judged to be cause of pain	Trial lasted up to 2 weeks After implantation of epidural catheter, assessed by behavioural medicine/psychology specialist
Wang, 1985[63]	62	Cancer	Injection	Morphine	0.7 mg[d]	Pain limited to pelvic or perineal area or lower extremities Other narcotics ineffective or intolerable side-effects Alternative therapies not contemplated No neurological or sphincter disturbances Life expectancy ≥ 2 weeks	Patients excluded if no pain relief at 2 mg or intolerable side-effects
Winkelmuller and Winkelmuller, 1996[65]	120	Non-cancer	Intrathecal infusion	Morphine	1 mg/24 h	Inability to treat pain successfully Somatic pain Unsatisfactory response to other routes or intolerable side-effects Failure of other pain therapy No psychiatric illness	Increase of morphine dose until satisfactory analgesia

continued

TABLE 37 contd *Details of studies using initial intrathecal trials of spinal opioids prior to pump implantation*

Reference	No. patients	Patient type	Type of trial	Drug used	Dosage	Criteria for inclusion	Notes
Wen *et al.*, 1985[100]	7	Cancer 4 Non-cancer 3	Lumbar	ß-Endorphin, dynorphin			Observed continuously for 1 h
Wen *et al.*, 1987[64]	6	Cancer	Lumbar injection	Dynorphin	7.5, 15, 30, 60 µg		Observed continuously for 1 h
Yoshida *et al.*, 1996[67]	18	Non-cancer	Intrathecal and epidural	Morphine	Intrathecal 1–2 mg Epidural 5 mg		Observed continuously for 1 h

[a] *Several patients received saline placebo*
[b] *To cisterna magna or lumbar theca*
[c] *Continuous epidural infusion was the most common type of screening (35.3%); bolus intrathecal injection 33.7%; bolus epidural 24.5%;. least common was continuous intrathecal infusion*
[d] *In debilitated patients, dose was 0.5 mg*

TABLE 38 *Types of trials for intrathecal administration*

Trial type	No. patients
Intrathecal bolus	649
Intrathecal infusion	166
Epidural bolus	240
Epidural infusion	232

TABLE 39 *Inclusion criteria in studies not utilising spinal opioid trials prior to pump implantation*

Reference	Inclusion criteria/comments
Yang *et al.*, 1996[66]	"Pain was of variable severity"
Hardy and Wells, 1990[36]	"Intrathecal [patient-controlled analgesia] was used in a series of eight successive patients"
Brazenor, 1987[22]	Pain unrelieved by conventional analgesics or presence of unacceptable side-effects No possibility that psychological factors were the cause Actual or impending blockage of subarachnoid space Life expectancy > 60 days
Ventafridda *et al.*, 1987[62]	Chronic cancer patients Non-responding patients because of inefficacy caused by intolerance to opioids
Devulder *et al.*, 1994[30]	Systemic and co-analgesics failed, or yielded intolerable side-effects[a]

continued

TABLE 39 contd *Inclusion criteria in studies not utilising spinal opioid trials prior to pump implantation*

Reference	Inclusion criteria/comments
Schultheiss *et al.*, 1992[56]	Other opioid therapy failed
Cheng *et al.*, 1993[24]	Inability to control pain in other ways Life expectancy > 3 months Pain-induced regions other than head and neck Intact family function
Gestin *et al.*, 1997[33]	Nociceptive or mixed nociceptive–neuropathic pain Various techniques had been tried Cell-destructive or neuroablative techniques failed
van Dongen *et al.*, 1993[61]	Inadequate pain relief or intolerable side-effects Oral medication was minor analgesics, NSAID or slow-release morphine tablets All other treatment ineffective
Muller *et al.*, 1988[44]	Insufficient efficacy of oral/parenteral therapy: intolerable side-effects > 6-month prognosis 1 week clinical treatment and evaluation of efficacy and dose finding (no further information)

[a] *Intrathecal route chosen above epidural because "analgesics administered epidurally are less potent and complications may be more frequent"*

Chapter 5

Costs

The validity of intrathecal pump systems is intrinsically bound up with issues of cost. Some systems, particularly type 5 programmable pumps, are costly and this is often cited as a reason for avoiding their use. However, there are many different factors apart from the actual cost of the pump that have to be taken into account when considering issues of costs and benefits.

There have not been any studies that compare the relative costs of the different pump systems with conventional analgesic treatments. Mathematical models and cost projections have been published but these are likely to apply only to the situation that pertains in a particular institution and may have only limited applicability in other clinical scenarios. The costs associated with intrathecal pump usage are:

- short-term economic considerations
  - purchase price of the pump system
  - hospital follow-up episodes including inpatient stays and outpatient appointments
  - drug costs
- long-term economic considerations
  - costs relating to time off work
  - disruption to life, and the psychological and debilitating costs of chronic pain.

There are four methods of establishing the cost-effectiveness of a therapy:[129]

- Cost minimisation: Costs and outcomes are assumed to be similar; the principal focus is on the medical costs of an intervention.
- Cost-effectiveness: There are two similar or broadly similar outcomes and the focus is on costs and effects.
- Cost–utility analysis: Costs are compared with quality outcomes; quality-adjusted life years are used as a measure of effectiveness.
- Cost–benefit analysis: An assessment is made based on all conceivable costs as well as all conceivable benefits.

All four of these methods are problematic because of the difficulties in assigning costs to the variables.

Evidence on costs and comparative costs from published studies

Cost modelling

- Hassenbusch and colleagues:[129] Using a cost-minimisation analysis, the costs of five different routes (including intrathecal) of morphine administration were projected by using mathematical modelling and then compared with each other. Cumulative costs of the different routes of administration crossed over or were comparable at different times in a patient's life, depending on a number of factors, including dose escalation and complication rates.
- de Lissovoy and co-workers:[130] This study used a cost-effectiveness analysis to compare the costs of intrathecal implantable pumps with conventional therapy for failed back surgery syndrome. Computer modelling of costs was used, and best and worst case scenarios were compared. These authors concluded that intrathecal therapy costs were less than conventional therapy costs after 22 months of treatment (US$82,893 compared with US$85,186).

Actual costs

- Hassenbusch and co-authors:[129] Details of a small group of patients receiving a type 5 pump were described. A reduction in the cost of health care over a 1-year period was reported.
- Muller and colleagues:[44] Actual costs of intrathecal treatment were assessed in this article (*Table 40*). In the analysis these authors combined data for the following patient and treatment types: epidural catheter and implanted pump (n = 18); implanted epidural catheter with port and external pump (n = 22); and intrathecal catheter and implanted pump (n = 23). It was not possible to determine the actual costs of intrathecal therapy from these data.
- Bedder and colleagues:[131] Type 5 pumps were compared with type 1 pumps. These authors showed that the initial cost of a type 5 system was high owing to purchase costs, but, after 3 months, the costs were lower than for type 1 because of the higher drug and dispensing charges associated with type 1 systems.

TABLE 40 *Costs from Muller* et al., *1988*[44]

No. patients	63
No. operations[a]	72
Total time in hospital	522 days
Ambulant treatment	10,505 days
Pump refills	572 times
Cost of materials	43,500 DM
Cost of clinical and ambulant care	22,500 DM
Cost per patient (average)	10,476 DM
Mean daily cost	60 DM

[a] *Operations for implantation of pump or port, or for surgical revision*

Chapter 6

Analysis of the robustness of the results

Type of evidence found in the literature

The vast majority of the substantial literature on intrathecal techniques is in the form of case reports and case series, the very type of evidence that is found at the bottom of the "hierarchy of evidence" table:

- systematic reviews and meta-analyses
- randomised controlled trials with definitive results
- randomised controlled trials with non-definitive results
- cohort studies
- case-control studies
- cross-sectional surveys
- case reports and case series.

The most apparent inadequacy in this review, one that is referred to unerringly throughout, is the lack of comparator trials. However, the use of intrathecal pumps in chronic pain is a difficult area in which to design such studies, principally because patients who are provided with this therapy are deemed to have exhausted all other types of treatment. Intrathecal therapy is therefore presented as the final and only option available. In such cases, randomisation to a different therapy could be difficult. However, we believe that some form of comparator trial is nearly always possible. In addition, randomised controlled trials on a very small scale, the "*n* of 1" studies, could be utilised more readily. Paice and colleagues[48] discussed the use of such a design. The fundamental principles are to ensure that blinding is effective amongst patients, administrators of the drug, and data analysers, and that the appropriate outcome measures are taken at predetermined times.

Analysis of "low-grade" evidence

Case reports and case series are ranked low in the hierarchy of evidence, but what is to be done with these studies? Are they to be ignored or is there still some place for them when evaluating the worth of a particular intervention? If they are to be included they need to be assessed; validation supplies some means of providing objective value.

The rules to be applied when dealing with randomised controlled trials are well established. The *JAMA* guidelines[132] are just one example of the help that is available to the clinician or researcher when attempting to assess the worth of a randomised controlled study. We decided that we would attempt to identify some factors that showed that there was an awareness of methodological issues on the authors' part and that this made the article a "better" one. We began the process of scoring by using a set of guidelines from the University of York.[133]

Assessing the rigour of longitudinal surveys or case series: York model

- Is the study based on a random sample selected from a suitable sampling frame?
- Is there any evidence that the sample is representative of standard users of the intervention?
- Are the criteria for inclusion in the sample clearly defined?
- Did all individuals enter the survey at a similar point in their disease progression?
- Was follow-up long enough for important events to occur?
- Were outcomes assessed using objective criteria?
- If comparisons of series are being made, was there sufficient description of the series and the distribution of prognostic factors?

We modified these guidelines to make them more applicable to this review on intrathecal therapies and then applied them to 49 case-series studies[19–67] to see which ones scored the highest. No single case reports were included. The number of patients studied ranged from two to 200 (mean 40; median 23). The questions contained in these guidelines aim to assess the quality of the case-series information. One point was allocated to each of the following questions (maximum score 16):

- Was the study based on an appropriate sample selected from a suitable sampling frame?
- Was there a statement to suggest that only patients with intractable pain were included?
- Did the article explain in detail what the selection criteria were?

- Was follow-up long enough for important events to occur?
- Were dose escalation details supplied?
- Were outcomes assessed using a VAS or similar objective measure?
- Were pre- and post-intervention VAS scores given?
- Was another objective outcome measure given?
- Was the same objective outcome measure given pre- and post-intervention?
- Was an additional one or more outcome measures given?
- Was the same additional outcome measure(s) given pre- and post-intervention?
- Was all the information on side-effects given?
- Were all the relevant complications shown in sufficient detail?
- Was there a trial of either epidural or intrathecal opioids prior to implantation?
- Was the trial blinded?
- Have the patients been incorporated into a clinical trial?

Results of the modified York scoring system for case-series studies

Using the York scoring system, the seven studies that scored the highest number of points (14) were: Anderson and Burchiel,[19] Hassenbusch and co-workers,[37] Sjoberg and co-authors,[58,59] Tutak and Doleys,[60] Winkelmuller and Winkelmuller[65] and Nitescu and colleagues.[89]

Conclusions

It is possible that by using the above scoring system for case series that the best reports can be identified. Perhaps it would then be appropriate to place more weight on the results of these studies.

Furthermore, it would be possible to design a case-series study that included all the information contained in the modified guidelines; this study could then be considered to be of good quality.

Chapter 7

Opinions on the efficacy of intrathecal pump systems: responses to a telephone survey

Need for a telephone survey of UK "experts"

An additional strategy was chosen to compensate for the paucity of the evidence, in terms of quality rather than quantity, in this systematic review. We decided to elicit personal opinions via a telephone survey from a range of users and non-users of intrathecal therapy. In essence, what we have done is to combine one set of "low-grade" evidence with another; personal opinion and anecdote are not dissimilar to case series. However, we considered that the inadequate evidence in the review placed us in unfavourable circumstances and it was necessary to redress this by ascertaining the views of current practitioners in the field. Those who have published in this subject area inevitably have strong, usually favourable, opinions of this treatment, but many of those we spoke to in this survey have not published their views. We wanted to ensure that we obtained a more balanced view within the context of users and potential users, enthusiasts and antagonists.

We decided to undertake a short telephone interview with them, an effective method whereby a specific target may be accessed and a large amount of information gathered rapidly.[134]

No apology is made for this method of interview because the survey was not intended to be a random sample of a statistically significant number, where exact questions and mannerisms on the interviewer's part are used to ensure equality of approach and lack of bias. The purpose of the survey was to engage in discussion and elicit as many views and ideas as possible on this technology. One useful by-product of the technique emerged in the discussion on the need for a registry or ongoing audit of intrathecal pumps to ensure that all faults and failures can be recorded objectively.

Sample

A group of 21 UK anaesthetists, palliative care consultants and pain management specialists who were considered (by two of the authors, JEW and GT) to be leading practitioners in the field were selected. All were contacted by a letter explaining the project and informing them that a Research Fellow would contact them for a short telephone interview. This took place with 18 participants. The length of the interview ranged from 10 to 25 minutes. One practitioner suggested that his senior registrar would be a more appropriate person to contact, which was done. Three were eventually excluded because it proved impossible to arrange a time to speak to them. One was not contacted because a previous meeting had taken place with him and his team. One other practitioner was contacted after a recommendation by a colleague during an interview.

Semistructured questionnaire

A semistructured questionnaire schedule was devised by the research team:

1. Are you using any intrathecal pumps? If no, go to 10.
2. If yes, what type of pumps?
3. What type of patients?
4. How long have you been using them?
5. Why did you decide to use them in the first place?
6. At what point in your treatment programme do you decide to use them?
7. Do you use a protocol or some form of guideline procedure to assist you in deciding when and with which patients you would use intrathecal pump systems?
8. How do you decide what dosage is appropriate?
9. What incidence of adverse effects would you deem to be acceptable – at the most extreme level?
10. Why do you not offer the therapy?
11. Do you think there is ever a role for intrathecal pumps? Could they ever be appropriate?

The interview schedule was not piloted but developed and expanded in response to issues that emerged. Thus, for example, when one practitioner suggested that companies that

manufacture and sell the pumps refuse to acknowledge the high level of failure of the pumps, opinion was sought from subsequent interviewees on this issue. Another question that was added early on in the process was whether the interviewees considered the therapy to be of historical interest only, with little or no current applicability. Views on costs were also elicited.

Results

Experience

By chance, the level of experience of using this therapy amongst the 18 interviewees was well balanced. Seven had no experience at all, six had some experience, and four used it currently. One has been excluded because the discussion with him rested solely on the need for a registry of pumps used and his experience of trying to establish one.

Attitude towards the use of intrathecal technology

Rather than a continuum of opinion, there seem to be three definite groups of practitioners: those against the therapy and those that favour them – almost a low-tech versus high-tech divide – and a group in the middle who accept them but are perhaps nonplussed. The spread amongst the interviewees covered this range equally, with five in the "against" group, five in the "for" group, and six in neither.

Feelings against the technology were rather strong. "I'm not sold on the idea", one said and continued: "I don't trust them one jot." One described himself as a Luddite and felt that he was "conservative and tax efficient". He, as others, felt that the need for this technology had been overtaken by the excellent palliative care facilities that are now available. Another described himself as "cynical", but suggested that his cynicism was well rooted in the motives of the people who use them (i.e. making a lot of money out of their use, particularly from private patients). One expressed suspicion that the technology is "driven by the industry". In line with a number of others, he confirmed that he would be "more impressed" by them were there more evidence of their efficacy. A number who either do not use them or have used them only sparingly in the past suggested that this is because their anaesthetists do not use them or because they simply do not see those patients whose pain is unable to be managed by the "gamut of pharmaceutical and non-pharmaceutical interventions". Only one came straight out and said his attitude was "positive".

Current status of intrathecal therapy

Interviewees were asked if they thought the therapy was of only historical interest, with little or no current applicability. Amongst those who answered this question there was an equal split: four agreed and four disagreed. Some were more vociferous in their agreement (e.g. one who said, "All treatments without diseases are passé eventually.") to those who agreed only vaguely (e.g. "There is an element of truth in this.") and went on to explain that "some therapies enjoy initial vogue". One participant suggested that she "wouldn't miss it if it were taken off the market". There was variability among those who disagreed with the statement: "I disagree entirely", "I don't think so", and the more ethereal: "This implies we have moved on to something better." One interviewee perhaps summarised the consensus view: "It is a niche treatment."

A shared opinion about why the therapy works was given by two interviewees. They both suggested that there is a strong placebo effect. One said, "The better the technology, the better the placebo effect." The other agreed: "There is a great placebo effect for patients and that is what intrathecal pump systems may be about." He concluded by questioning: "Has anyone shown that sterile saline works?"

Patient selection

There were three main areas of patient selection:

- cancer versus non-cancer pain
- nociceptive versus neuropathic pain
- duration of illness.

Although one interviewee said that intrathecal pump systems are **not** justified in cancer pain because of the expense, seven specifically said that they would use them **only** for cancer patients. One suggested that they could be used for both types of patients as long as the source of the pain was nociceptive. Another suggested it should target neuropathic pain. One suggested that, of the 500 new pain patients he sees every year, only three to four have pumps, with one to two of these for patients with non-malignant disease.

There was, however, broad agreement on duration when it was mentioned. Two suggested that the prognosis must be "long", or "long enough to justify the use"; one specified more than 3 months and one between 4 and 6 months.

Protocols and trials

Of the four practitioners who spoke of protocols and guidelines for clinical use, none used

protocols in their practice. "There is nothing written", one said. "There is an understanding that patients have a prognosis of 6 plus months, that pain is not responsive, they have side-effects and appropriate adjuvant analgesia has been tried." He however cautioned: "They must be psychologically up to the device, not overwhelmed by anxiety. They must be able to use the device properly." The psychological angle was discussed by another: "If the patient is stable psychologically."

Only two practitioners spoke of assessing patients to ascertain their suitability for the treatment. One said she didn't use "specific tools"; she does, however, "speak to the patients and the people who refer them" and "listen to them for their aims and objectives and look at their history". The second interviewee reinforced the need to "look at the psychological state". He suggested that assessment was mainly down to "gut feeling".

One practitioner based decisions for inclusion on "clinical knowledge". He suggested that, as he was the only one using them in his particular hospital, he was in a position to know when pain was not controlled. He did not like using protocols because "it stops people thinking", although there was a protocol for nurses. Another also spoke of the "danger of protocols", because they drive people to "irrational decision making – making decisions for the wrong reasons". One person objected to the term protocol and instead spoke of producing "clinical consensus statements". He defined their needs as wanting "diagnostic criteria which they can agree upon and treatment criteria". They needed "an algorithm of sorts" but without rigidity.

One consultant spoke of single-shot intrathecal trials of therapy in a previous practice and said that efficacy and volumes were worked out to check if the route was acceptable and practical, only progressing to pumps once the trial was successful. Another, who also undertook trials, uses bupivacaine and opioids and assesses over a few days "for analgesia and acceptability, and then decides".

Epidural versus intrathecal route

Six practitioners voiced a distinct preference for the epidural over the intrathecal route: "Epidurals are effective enough", "Epidurals are more versatile, no need for intrathecal pumps", "Epidurals can be used for cancer pain with relatively few problems", "We've had considerable success with epidurals," and finally: "We use epidurals rather than intrathecals because they are as effective in most cases." Some compared the two: "There aren't more problems with intrathecals but there are technical problems including blockages" and, "With epidurals you can go as far as T6 or T4 but with intrathecals you can go as high as you like." One suggested that with epidural injections patients develop localised infections, but with the intrathecal route infections are more generalised. Only one made a positive comparison with the epidural route: "Intrathecal has lower volumes, which is better."

Side-effects

The issue of side-effects was considered to be important and we were advised to attempt to establish the outer limits of acceptability of adverse effects. One consultant gave a conservative estimate of the extremes of acceptability: "Acceptable side-effects are those that are acceptable for any intrathecal administration (i.e. drowsiness while getting the dose right, weakness in legs)," and: "While urinary retention is acceptable, this would not be so of respiratory depression." Another, however, said, "Respiratory depression would not put me off."

Many practitioners spoke of the problems of infection: "The biggest worry is infection." There is a "significant risk of infection and need to replace them [the pumps]" and a "great risk of infection [in epidural and intrathecal administrations]". One said that he had not had an incident of infection in the previous 5 years and that he had inserted a considerable number of pumps, although he confirmed that he used totally implantable systems "which are less liable to infection". An interviewee spoke about the problems of infection but suggested that "it usually settles". Another was "aware of one person who said that 40% of his intrathecal catheters had to be removed because of problems of infection". A practitioner who was gravely concerned about infection said that he always inserts pumps in theatre "under sterile conditions". He spoke of the Japanese who have "large numbers of intrathecal catheters and they reckon after 3 to 4 months they are all infected and they treat patients with antibiotics". He suggested that it is more important to "work to reduce the incidence of infection". Conversely, one said she was "not concerned about infection".

There were other issues, from the less serious to the more so. One consultant spoke about a patient who could not come to terms with the reservoir and was distressed by the patient-activating button, and another who became frightened by the lack of sensation in his legs. She suggested it was "common to see distressing sharp radicular pain on injection when pressing". Another spoke of

common problems such as "headaches, pump dislocation, haematomas, abscesses". More serious problems included meningitis: "One patient got meningitis after 2 years." One participant said that "all those who used pumps ended up with meningitis but that was because the patients injected themselves and didn't develop sterile techniques". This was reinforced by an experienced consultant whose patients had developed meningitis: "All meningitis cases were with reservoirs and top-ups where they [the patients] or a nurse injects." He taught the patients to look out for the symptoms. One practitioner said he had seen no incidents of meningitis.

Another issue that was discussed briefly was tolerance and addiction. One practitioner said that "tolerance occurs in some but not in others" and that "addiction is a problem but not necessarily with intrathecal". Another spoke of his experience of tolerance in one patient.

Clearly, these practitioners had very different experiences. One had "not come across serious life-threatening side-effects" and another believed that "side-effects and adverse effects make it [the treatment] inappropriate".

Risks

Interviewees were asked what level of risk they would deem to be acceptable. Although one stated categorically that "risk can't be justified", others were more expansive:

> The extent of the risk is directly related to the severity of the person's pain. If it is unliveable with, intolerable, then they would take higher risks. If pain is reasonably well controlled but the patients don't like taking pills then any unreasonable side-effects would not be acceptable. Pain would need to be very severe to risk meningitis.

Another was prepared to put a figure on the risk: "Amongst patients with benign pain, an incidence of 1/1000 meningitis is not acceptable, but in a cancer patient 1/100 is acceptable." One interviewee suggested that the risk is related to the duration of treatment and emphasised the importance of discussing this with the patients themselves. He said that some patients are "risk averse, and some are gung-ho. Some believe no risk is ever going to happen to them [the patients]".

Problems

Problems were related to negative experiences by individual patients or practitioners, to hearsay problems or to gossip, such as one who suggested that "a series of patients have died with one practitioner". However, the problem of failure or even death was addressed by two interviewees. One spoke of his experiences while attempting to set up a registry of such failures, and another said, "There is no information kept on how many are used and removed or the complications of removal. There is no audit."

Others dealt with the problems associated with a difficult technique that demands heavy resourcing of experienced and skilled practitioners. One said, "Carers in the community aren't geared up to dealing with intrathecal devices. There is a lack of training, knowledge, skills and attitude amongst health professionals in the community." Another suggested that doctors are "never quite as slick" at inserting the catheter most efficiently: "The process of implanting can be distressing for patients who are distressed anyway." One practitioner spoke of the problems of refilling pumps and that there is "not much leeway with intrathecal pumps". He mentioned the dependence on "highly skilled doctors" and that "if patients are at home they are dependent. They can't just go off on holiday."

Drugs and dosages

Not much was said about drugs, although one consultant spoke of the need to "look at new drugs". He said that he used to use only morphine but that he now uses "2% lignocaine and often clonidine". He urged people to look at ketamine, DADL and NMDA (i.e. *N*-methyl-D-aspartate) inhibitors as well, because "they may all be relevant by the intrathecal route".

There were some contradictory opinions on dosages. Although all who spoke of this agreed that the intrathecal dose depended on the oral start dose, some divided the oral dose by 1/100th to yield the intrathecal dose and others by 1/50th. One mixed the dose with bupivacaine and adjusted it on the basis of side-effects.

Costs

All the interviewees had an opinion on the economic factors. These ranged from "it's not economically viable" and "it's out of the question" to "it's not an issue" and "costs would not be an issue with appropriate patients". The argument for viability covered the following points: "They are very cost-effective compared with the price of overnight stays and the cost of devices trying to control pain. We save on outpatient appointments and hospital admissions. Money can be recouped"; "The cost of pumps is not greater than the cost of a neurosurgical operation"; and "The cost of 5000

[pounds] for programmable pumps versus hip replacements does not sound unreasonable if the outcomes are good." Some look at cost within the context of the duration of treatment: "If the patient has it in for 40 days the cost is not an issue"; and "Costs are reasonable with the 3-month rule." Some see the cost as justified "in the right patient".

However, many see the biggest problem as persuading the health authority or insurers to pay: "Lots of problems with the health authority and a good case must be made"; "Insurers don't want to pay. They see it as palliative"; and "We take it to the purchasers on a one to one basis. They decide."

Other practitioners made comments such as: "Cost is not what matters – quality of life is." Some suggested that cost factors are relevant but they would "already have gone through the cheaper alternatives". Some were averse to spending money on this therapy when so little evidence of efficacy exists. One suggested that there are much cheaper alternatives: "Graseby pumps are much cheaper and re-usable." He compared the cost of "4 to 5 thousand [pounds] compared with percutaneous [administration], which may cost from £100".

Centres of excellence

A suggestion that was made by three consultants is the need to have recognised centres of excellence undertaking the work of implantation: "It should only be done in a few centres"; "Some centres should do it but not everyone"; and "There is a desperate need to have recognised centres with [staff with] adequate expertise doing them." The third consultant continued to suggest that they should not be done until there is "clear evidence of benefit" and that "patients should only have them done as part of a formal research programme, which should be multi-centre." He suggested that only those "with expertise and low complication rates are given funding and resources to do proper studies" and that there is "independent monitoring of outcomes and adverse events to ensure observer bias is eliminated". One consultant suggested that doctors "should have to satisfy credentials that they can undertake certain procedures".

Evidence for effectiveness

The need for evidence was a clarion call by a number of practitioners: "There are no trials comparing intrathecal techniques with less invasive technologies"; "The HTA should make it clear that they would like further studies. It is no good to say it is not effective when one doesn't know if it is or not"; "[There is] not enough evidence. There are case reports but no randomised controlled trials"; and finally, "[There is] not sufficient evidence of benefit."

Conclusions

The variety of opinion about intrathecal therapies that is evident in this report is not represented in the literature; for this reason alone it is a valid survey. The risks of the therapy, so few of which are discussed in published studies, are forcefully suggested here.

The need for a centralised registry of the devices used in this therapy has become apparent. This would ensure that the objective results of failures and complications are available to anyone, practitioners and patients alike, who requires outcome information prior to making choices on the use of intrathecal pumps.

Chapter 8

Discussion and conclusions

The overwhelming bulk of the poor-quality evidence gathered in this review demonstrates the effectiveness of this form of treatment. All the case series and reports that evaluated intrathecal opioid treatments showed analgesic benefit but we found no evidence that this form of therapy is superior to existing analgesic treatments such as tablets or injections. In addition, the positive effects reported in the literature were not matched by the opinions of individual practitioners when asked in a telephone interview.

The main difficulty with drawing conclusions is that we are reporting on the effect of many different interventions (pump types and drugs) in many different patient types, measured using a variety of non-standardised outcome measures over a variable time.

From this heterogeneous mixture of populations interventions and outcomes we have tried to draw out some themes in an attempt to answer questions about effectiveness versus risk. However, the data are low grade, falling at the bottom of the hierarchy of evidence. This report does not attempt to legitimise these data or to push them up the quality ladder.

Reporting of the effectiveness of intrathecal pumps needs to be clearer, with more detailed description of the population type and the specific intervention used (pump and drug type), and must use standard outcome measurements over a suitable follow-up period.

In an attempt to clarify the clinical situation it may be helpful to divide the patients into two broad clinical groups. In group 1 patients, the therapy really is a last resort intervention and it would usually be difficult to randomise these patients into a non-intervention group. This type of patient will typically have intractable pain due to cancer and will have a limited life expectancy. Group 2 patients have a long-standing pain problem and, although many previous treatments have been tried and failed, it would still be appropriate to include them in a randomised controlled trial.

The characteristics of group 1 patients are:

- limited life expectancy
- usually but not exclusively cancer pain
- all conventional therapies have failed
- intractable unrelieved pain
- simple, low-cost, implantable pump system may be appropriate
- implantation procedure performed locally
- proper measurement of effect (beneficial and adverse) using standardised outcome measures is appropriate and possible
- registry of pump usage is appropriate and possible
- randomised controlled trial of pump versus no pump treatment is probably **not** appropriate.

The characteristics of group 2 patients are:

- unlimited life expectancy, usually greater than 1 year
- usually but not exclusively non-cancer pain
- many conventional therapies have failed
- systematic patient selection criteria have been applied
- totally implanted system may be appropriate
- registry of pump usage is appropriate and possible
- randomisation into treatment with implantable system or further application of non-invasive conventional treatments **is** appropriate.

Further categorisation of the intervention used and outcome measures would also need to be described.

One study evaluated intrathecal therapies on cancer and non-cancer patients[28] and concluded that they were not recommended for non-cancer patients. Four out of five studies evaluating intrathecal therapy in non-cancer patients in our series did show some beneficial effect. The authors of one study on non-cancer patients stated that the risks outweighed the benefits.[67]

The most commonly used drug was intrathecal morphine with or without bupivacaine or clonidine. Dose escalation was reported to be an issue and may be caused by the development of true tolerance or be due to other factors. Tolerance was overcome by simply increasing the drug dosages and was not a major issue with most practitioners.

Two main risks occur with intrathecal pump systems:

- Pharmacological side-effects of the particular drugs used were reported in 3–26% of patients.

- Mechanical complications associated with the specific device used were reported in up to 25% of patients.

It has not been possible to assess the magnitude of the various side-effects or to distinguish between the pump types. These figures may seem high, but the population in question might already have received many different drug treatments without much success.

Numerous criteria are used to assess patient suitability prior to intrathecal therapy. The most comprehensive programmes use well-designed protocols and trials of therapy before implantation.

Very little evidence emerged on the comparative costs of intrathecal pump systems and conventional analgesic therapy. However, a number of cost-modelling projections may indicate some cost–benefit at varying times after the initiation of therapy, depending on individual patient circumstances.

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.

Implications for healthcare

- Intrathecal pump systems may be effective in treating chronic pain but good comparative evidence of effect and side-effects is currently lacking.
- The evidence from this review reveals that a wide variety of intrathecal pumps and drugs are used in different types of patients, and that numerous outcome measurements are made after variable follow-up periods.
- In view of the lack of comparator data, we believe that further use of this form of intervention is inappropriate in group 2 type patients unless it is as part of a comparator trial with conventional analgesic therapies. In group 1 type patients, who have limited life expectancy, such trials are more difficult to implement. However, we would recommend that, at the very least, standard assessments are made in these patients to gauge efficacy and risk.

Recommendations for further research

Further information is required before definite recommendations can be made.

- Two types of further information could be obtained with relative ease:
  - data from randomised controlled trials of implantable intrathecal pumps versus conventional therapy
  - establishment of a database of pump usage, with data being collected using standard outcome measures
- Further research should clearly delineate the following variables:
  - population type: divided broadly into two groups (i.e. patients with limited life expectancy and patients with near normal life expectancy)
  - intervention: pump type, drug type and dosage clearly described
  - standard outcome measures: to quantify effect and side-effect changes before and after intervention
  - follow-up measurements and details of costs.

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We look forward to hearing from you.

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