Original Manuscript

THE BRITISH PAIN SOCIETY
EXPERTISE WHERE IT MATTERS

British Journal of Pain
2024, Vol. 0(0) 1–26

DOI: 10.1177/20494637241280356
journals.sagepub.com/home/bjp
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Intrathecal drug delivery for the management of pain and spasticity in adults: British Pain Society's recommendations for best clinical practice

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Abstract

The British Pain Society updated their recommendations on intrathecal drug delivery (ITDD) for the management of pain and spasticity in adults. The recommendations are primarily evidence based but where necessary comprise the consensus opinion of the working group. The recommendations are accompanied by information for patients and their carers, intended to inform and support patients in their decision making. The updated guidance includes recent evidence base of ITDD use in pain and spasticity, address the issues of drug pump compatibility following the latest manufacturer and Medicines and Healthcare products Regulatory Agency (MHRA) recommendations as well as provide an update on the indications and complication management particularly endocrine complications and intrathecal granuloma formation.

Keywords

Best practice recommendations, intractable, intrathecal drug, chronic pain, spasticity

Introduction

The technique of intrathecal drug delivery (ITDD) is based on the principle that effective analgesia can be achieved by the action of some drugs at the dorsal horn of the spinal cord where adequate concentrations cannot be achieved by systemic administration, or only by high systemic doses. Delivery of the drug by the intrathecal (spinal) route is a means of achieving enhanced therapeutic effects. The smaller doses needed for intrathecal administration also allow a reduction in side effects compared to

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systemic administration. There is evidence to support this technique.

This document is intended to define and support best practice and provide guidance for:

- practitioners and institutions delivering or planning to deliver the treatment
- referrers, as to which patients might benefit
- primary carers regarding the management of patients with implanted ITDD systems
- purchasers of health care as to the nature of the technique and when it might be used.

The document describes the clinical use of ITDD systems in the management of pain and spasticity, reviews the available drugs and ITDD technologies and provides recommendations for the context in which this therapy should be delivered. It covers the situations in which pain relief is the major indication for the technique.

This update aims to include recent evidence base of ITDD use in pain and spasticity, address the issues of drug pump compatibility following the latest manufacturer and Medicines and Healthcare products Regulatory Agency (MHRA) recommendations as well as provide an update on the indications and complication management particularly endocrine complications and intrathecal granuloma formation.

Methods

The recommendations are primarily evidence based but where necessary comprise the consensus opinion of the working group. The recommendations are accompanied by information for patients and their carers, intended to inform and support patients in their decision making.

Members of the update working group were chosen for their clinical and research expertise in the topic of ITDD and familiarity with the peer-reviewed literature. The group conducted an up-to-date review of the evidence relating to ITDD in order to update the British Pain Society guidance (version December 2015) with the most up to date evidence and consensus-based recommendations where it was felt that changes were relevant to UK and Ireland ITDD practice. Where the working group felt that recent evidence may not impact UK and Ireland practice the evidence was cited with no recommendation made.

Executive Summary

- Intrathecal (spinal) drug delivery can be an effective method of pain control; it has a supportive evidence base.
- There are three major indications namely:
  - chronic non-malignant pain (CNMP)
  - pain associated with cancer
  - spasticity
- For CNMP there are large scale randomised controlled trials (RCTs) relating to the use of ziconotide and two supportive small RCTs as well as several prospective single-arm studies.
- For pain in patients with cancer, there is RCT evidence.
- For spasticity, there are well designed single-arm studies in adult and paediatric populations for clinical and cost effectiveness assessment. There is RCT evidence for stroke related spasticity.
- Patient selection is important, particularly when used for CNMP. This technique must be provided by a multiprofessional team with a comprehensive understanding of the physical, psychological and rehabilitation aspects of the patient's condition.
- A multiprofessional, relevant infrastructure must be provided for continuing care.
- A range of alternative treatments with appropriate support for their delivery should be available and considered.
- Adherence to best practice is essential. Uniformity of best practice should be encouraged; this does not limit development in the use of the technique.
- Safety is paramount. The working group strongly support research and future work into design of delivery systems and equipment safety.
- It is the opinion of the working group that ITDD is an underused technique in cancer pain and spasticity and should be made more widely available. Its use in CNMP requires thorough patient information, evaluation and understanding of the long-term outcomes and potential complications.
- The distinction between the use of ITDD in cancer related pain and CNMP relates primarily to concerns about the potential consequences of long-term IT opioid administration (e.g. tolerance, granuloma formation, lower limb oedema and hormone suppression). In this respect people with cancer with a near normal life expectancy should be counselled as with CNMP patients.

Scientific rationale

Use in pain associated with cancer and CNMP

Opioid receptors were identified in the spinal cord in 1973.[1] Subsequent animal studies demonstrated that

intrathecal opioids produce powerful and highly selective analgesia.[2] Cousins in 1979[3] used the phrase 'selective spinal analgesia' to describe the phenomenon that spinally administered opioids could produce a specific analgesic effect with few motor, sensory or autonomic side effects. The first clinical use of epidural[4] and intrathecal opioids[5] followed. It was subsequently demonstrated that the analgesic effect was, in the main, due to the uptake of the opioid directly into the spinal cord and cerebrospinal fluid.[6] Intrathecal opioids exert their analgesic effect pre and post synaptically by reducing neurotransmitter release and by hyperpolarising the membranes of neurones in the dorsal horn, thus inhibiting pain transmission.[7]

Intrathecal local anaesthetics exert their effect by sodium channel blockade, which inhibits the action potential in neural tissue in the dorsal horn,[8] producing a reversible analgesic effect. They also have an action on the intrathecal part of the nerve root.

Intrathecal clonidine, an α 2 agonist, modulates pain transmission by depression of the release of the C fibre neurotransmitters, Substance *p* and Calcitonin Gene Related Peptide (CGRP).[9] It has been hypothesised that clonidine also suppresses preganglionic sympathetic outflow.

Ziconotide is a calcium channel antagonist specific to the calcium channels found at presynaptic terminals in the dorsal horn of the spinal cord.[10] Intrathecal ziconotide is thought to produce its analgesic effects by blocking neurotransmitter release in primary nociceptive afferent fibres.[11]

Use in spasticity

Intrathecal baclofen is used in the treatment of the severe pain and disability secondary to spasticity. Pain results directly from muscular spasm and indirectly from skeletal deformities. In spasticity, there is an imbalance between active and passive muscles due to a failure of γ-aminobutyric acid (GABA) mediated inhibition. Baclofen (a GABA agonist) restores the balance.

Evidence for effectiveness

Chronic non malignant pain (CNMP)

Several systematic reviews have assessed the clinical effectiveness of ITDD for the management of CNMP.[12–16] Most available systematic reviews are now over 10 years old and none of these reviews identified RCTs evaluating the effectiveness of ITDD for CNMP. The most comprehensive of these reviews (search of 10 bibliographic databases with no language restriction and complemented with hand search of reference lists and grey literature) suggested that based on the evidence available, patients who are able to continue on opioids long-term experience clinically significant pain relief.[15] This review observed a pooled baseline pain score of 8.70 (95% CI: 8.37 to 9.04) which at the longest duration of treatment (6 months to a mean of 29 months) decreased to 4.45 (95% CI: 3.44 to 5.47). The proportion of patients undertaking ITDD that achieved at least 50% pain reduction was 44.5% (95% CI: 27.2% to 63.2%).

Additional observational studies have been published since with follow-up periods ranging from 3 years to a mean of 13 years.[17–20] The morphine dose escalation was found to significantly increase throughout the 3-year period in one of the studies.[17] Two prospective studies observed that intrathecal morphine dose escalation stabilised between 24 and 36 months[18] and after 36 months post-implantation.[19] A prospective study of low-dose intrathecal opioids in the management of 61 chronic non-malignant pain patients reported a statistically significant reduction in both worst and average pain from baseline (8.91 and 7.47 at baseline) to (4.02 and 3.41, respectively, at 36 months) with an intrathecal morphine dose of 1.4 morphine equivalent/day at 6 months and 1.48 at 36 months.[18] Oral opioid averaged 128.9 mg of morphine equivalent/patient/day at baseline to 3.8 mg at 36 months.[18] Duarte et al. followed up a cohort of 20 patients with chronic non-cancer pain treated with IDDS for an average 13 years.[19] Statistically significant improvements were observed for the following sensory and psychosocial variables: pain intensity, pain relief coping, self-efficacy, depression, quality of life (QoL), housework, mobility, sleep and social life between baseline and 4-years data. No statistically significant changes were detected between assessments at averages of 4 and 13.5 years.[19] A prospective cohort of subjects (n = 58) enrolled following trial, in low-dose opioid therapy via an ITDD system reported significant improvements in visual analogue scale (VAS) and pain interference at 36-month with a mean intrathecal dose of less than 350 mcg morphine equivalent per day.[20] The authors observed that nociceptive pain responded better to low dose opioid therapy compared to mixed neuropathic/nociceptive pains.

In an RCT addressing the effectiveness of intrathecal morphine directly, Raphael et al. aimed to investigate the efficacy in the long-term by hypothesising that a reduction of the intrathecal opioid dose following long-term administration would increase the level of pain intensity.[21] Fifteen patients were randomised to intervention (20% dose reduction n = 10) or

control (n = 5). Owing to increasing severity of pain, seven patients in the intervention arm withdrew from the study prematurely. The VAS change between baseline and the last observation was greater in the in the intervention group (Mdn = 30.5) than in the control group (median, Mdn = 11), although not statistically significant, Z = −1.839, p = .070; r = −0.47. Within-group analysis showed that the VAS score was significantly lower at baseline (Mdn = 49.5) than at the last observation (Mdn = 77.5) for the intervention group, Z = −2.805, p = .002; r = −0.627 but not for the control group (p = .188). These findings are based on a small sample (n = 8) conducted at a single centre.

A recent parallel group RCT randomised 54 CNMP patients to either ITDD (n = 26) or conventional medical management (CMM) (n = 28), following a successful intrathecal trial.[22] Subjects were followed-up at three, six, nine and 12 months. The majority of the ITDD group (88%) received monotherapy of whom 66% received intrathecal morphine. Improvements in pain were noted across all time-points for the ITDD group, as compared to CMM, with significant improvements noted at the 3-month timepoint only. There was evidence of significant improvements across all the domains of the PROMIS-29[23] in the ITDD group, as compared to the CMM group at the three-month assessment. The attrition observed in this RCT was considerable which limits the interpretation of the study findings at follow-ups later than three-months. Only three patients randomised to ITDD, and two patients randomised to CMM were retained in the study at 12 months. Nevertheless, the study provided valuable lessons for the design of future RCTs which are still required in this space.

The rate of discontinuation of intrathecal opioid therapy due to unsatisfactory pain relief or adverse side effects is lower (17%) when compared with the discontinuation rates of oral opioid (45%) or transdermal opioid therapy (25%).[24]

Two randomised double-blind placebo-controlled trials of intrathecal ziconotide for the management of CNMP observed significant pain relief with average reductions in pain scores of 15%[25] and 31%.[26] Short-term (4 to 12 weeks) observational[27] and open-label studies[28,29] have assessed the safety and efficacy of combining intrathecal ziconotide with opioids for CNMP. Significant pain relief was observed with the combination of these drugs in patients who had inadequate analgesia with intrathecal opioids[27,28] or ziconotide.[29] An open-label, long-term, multicentre, observational registry of 93 adult patients with severe chronic pain receiving ziconotide either as first intrathecal agent in pump or not first intrathecal agent observed greater improvement in pain scores when ziconotide was introduced as first intrathecal agent, with most common adverse events being nausea, confusional state and dizziness.[30]

In Complex Regional Pain Syndrome (CRPS), van Rijn et al. conducted a single-blind, placebo-run-in, dose-escalation study in 42 CRPS patients to evaluate whether dystonia responds to intrathecal baclofen.[31] The dose-escalation study showed a dose-effect of baclofen on dystonia severity in 31 patients in doses up to 450 mcg/day. Thirty-six of the 38 patients, who met the responder criteria received a pump for continuous intrathecal baclofen administration and were followed up for 12 months to assess long-term efficacy and safety (open-label part of the study). Intention-to-treat analysis revealed a substantial improvement in patient and assessor-rated dystonia scores, pain, disability and QoL at 12 months.

Two double-blind crossover RCTs evaluated the effect of a 2- and 4-fold increase in the daily volume infused while keeping drug dose constant using baclofen in CRPS patients and opioid/clonidine bupivacaine combinations in chronic non-malignant pain patients.[32,33] Both studies concluded that under a fixed daily dose, a four-times higher infusion rate enhances the intrathecal distribution of drugs as evident from the significantly higher number of adverse events and drop in QoL but did not result in improved pain relief.

A further double-blind crossover RCT compared intermittent boluses to simple continuous infusion on patient's global perceived effect in ITDD for pain.[34] Thirty-two patients were assigned to receive their original daily dose of intrathecal medication either by simple continuous infusion followed by intermittent boluses or the opposite sequence for a duration of 4 weeks. Twenty eight of 32 participants completed both boluses and simple continuous infusion sequences and two patients completed at least one sequence. No significant difference was observed on the Patients' Global Impression of Change (PGIC) scale or pain scores between both administration modes. Patients receiving bupivacaine were more able to correctly guess the bolus sequence. An exploratory analysis indicated a trend toward a greater proportion of positive responders (improved PGIC) and lower pain scores with low flow rates.

Summary. The working group believes that there is mounting evidence of the effectiveness of ITDD in patients with CNMP. Large scale RCTs of ITDD in CNMP have shown limited short-term efficacy of ziconotide. Small RCTs support the efficacy of intrathecal opioids at 3-months follow-up and in

long-term patients while numerous prospective studies show long-term efficacy. The place of low dose ITDD opioids (micro dosing) and low flow rates in practice is yet to be established.

Pain in patients with cancer

Evidence from a Cochrane systematic review, two recent systematic reviews with meta-analysis and a Canadian Health Technology Assessment supports the use of intrathecal opioid therapy for pain that has not been adequately controlled by systemic treatment.[35–38] There has been one RCT study describing superior efficacy of intrathecal drug delivery compared with conventional medical management.[39] There are numerous case reports and case series describing the efficacy of neuraxial drug delivery in adult cancer patients. Evidence on the use of IDDS for the management of cancer pain in children is limited to 5 case reports and 1 case series for a total of seven patients.[40] All the seven patients included in the studies reported improved functional outcomes after IDDS implantation, such as returning to school and participating in physical activities.

Smith and colleagues in a multicentre, international, RCT showed improved QoL, by reason of pain control, and significantly less drug toxicity with intrathecal drug delivery compared to comprehensive medical management.[39,41,42] Although longevity was not an outcome measure, it was observed that at 6 months 53% of the ITDD arm were still alive compared to 32% of the conventional medical management group based on an 'intention to treat analysis'.[41] Mobility and alertness among other reasons may contribute to an improvement in longevity. Preclinical evidence shows morphine to be immunomodulatory,[43] yet these effects can be anti-cancer as well as cancer promoting. There is paucity of clinical evidence of a definitive cancer promoting effect of opioids, although much of that scant evidence is from comparison of intrathecal opioid delivery with systemic administration. Further research would help elucidate if there is a true survival advantage of intrathecal opioids.

One RCT demonstrated the usefulness of intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS.[44] Moderate to complete pain relief was reported with an average reduction in pain scores of 53%. A prospective observational study of 20 cancer patients with bone metastases involving the spine were treated with morphine/ziconotide combination.[45] The mean daily baseline VAS pain score at rest was 90 ± 7. The percentage change in VAS mean scores from baseline to 2 days, 7 days and 28 days were 39 ± 13% (95% confidence interval [CI] = 13.61–64.49, $p < 0.001$), 51 ± 12% (95% CI = 27.56–74.56, $p < 0.001$) and 62 ± 13% (95% CI = 36.03%–87.89%, $p < 0.001$), respectively.[45] A cohort study with cancer pain patients ($n = 77$) using a low starting dose of ziconotide in combination with morphine, clonidine and ropivacaine, and a slow upward titration regimen showed a mean decrease in pain intensity of approximately 48% from baseline.[46]

Summary. The working group believes that there is reasonable evidence supporting the use of ITDD in patients with cancer pain where this is not controlled by systemic analgesia or where systemic analgesia causes intolerable side effects.

Spasticity

Spasticity can arise from a number of pathologies, all of which include elements of upper motor neurone damage. Good evidence exists for the treatment of spasticity with intrathecal baclofen in multiple sclerosis, cerebral palsy and spinal cord injury.[47–52] One long-term multicentre randomised double-blind placebo-controlled study reviewed 93 patients with intractable spasticity due to either spinal cord injury (59 cases), multiple sclerosis (31 cases) or other spinal pathology (three cases).[52] They were entered into a screening protocol of intrathecal baclofen test injection. Of the 88 patients who responded to an intrathecal bolus, 75 underwent implantation of a programmable pump system for chronic therapy. After a mean 19 months (range 5 to 41 months) follow-up after surgery, rigidity was reduced from a mean preoperative Ashworth scale (AS) score of 3.9 to a mean postoperative score of 1.7. In addition, muscle spasms were reduced from a mean preoperative score of 3.1 (on a four-point scale) to a mean postoperative score of 1.0. Drug tolerance was not a limiting factor in this study despite an increase of the dose of intrathecal baclofen being required to control spasticity over time.[52]

For spasticity in stroke, a phase 4, randomised, controlled, open-label, parallel-group multicentre study compared ITB therapy versus CMM with oral antispastic medications.[53] Poststroke patients with spasticity in ≥2 extremities and an AS score of ≥3 in ≥2 affected lower extremity muscle groups were randomised (1:1) to ITB ($N = 31$) or CMM ($N = 29$). Forty-eight patients completed the study (24 in each arm). The primary analysis of change in AS at 6-months showed a significant effect of ITB therapy over CMM (mean AS reduction −0.99 (ITB) versus −0.43 (CMM); Hodges−Lehmann estimate, −0.667 (95.1% CI −1.0000 to −0.1667); $p = .0140$). There was a higher incidence of adverse events while receiving ITB

(24/25 patients, 96%; 149 events) compared with CMM (22/35, 63%; 77 events). The adverse events were generally consistent with the known safety profile of ITB therapy.[53] Secondary outcome measures observed significant treatment effects in favour of ITB over CMM for changes from baseline to month six in NRS for actual pain (ITB vs CMM: mean, −1.17 [SD, 3.17] vs 0.00 [3.29]; median, −1.00 vs 0.00; $p = .0380$) and least pain (mean, −1.61 [2.29] vs 0.24 [3.07]; median, −1.00 vs 0.00; $p = .0136$), and EQ-5D-3 L utility scores (mean, +0.09 [0.26] vs +0.01 [0.16]; median, +0.07 vs 0.00; $p = .0197$).[54]

Summary. The working group believes that the role of intrathecal baclofen is well established in the management of both cerebral and spinal spasticity. NHS England recommends the use of intrathecal baclofen in wheelchair bound patients with spasticity that is non-responsive to systemic medication.

Cost effectiveness

A variety of full economic evaluations have investigated the costs and benefits associated with the use of intrathecal morphine for CNMP.[55–58] These studies have considered ITDD to be a cost-effective alternative to conventional medical management for CNMP despite the high initial cost due to the pump device. The only UK based study with patients being administered intrathecal morphine has found ITDD to be within the NICE willingness to pay threshold of £20,000−£30,000 per quality-adjusted life year (QALY).[57] A systematic review of economic evaluations observed that ITDD for patients with CNMP would only not be cost-effective in extremely conservative scenarios.[59]

A cost-utility analysis for intrathecal ziconotide use in CNMP was carried out in the UK.[60] The cost-effectiveness of ziconotide when compared with best supportive care was £27,443 per QALY (95% CI £18,304-£38,504). A sensitivity analysis using the lower and upper bounds of the average ziconotide dose changed the incremental cost-effectiveness ratio to £15,500 [95% CI £8206−£25,405] and £44,700 [95% CI £30,541−£62,670]. A budget impact analysis observed that the estimated 5-year cumulative budget impact of treatment with ziconotide combination therapy for a 5-year time horizon was £2,487,539, whereas that of morphine monotherapy was £913,804.[61] The additional costs in any of the first 5 years were below the resource impact significance level of £1 million for medical technologies in England.

ITDD has also been found to be a cost-effective alternative to systemic, intravenous or external infusion devices for cancer patients who require pain management for 3 months or more.[38,62–65]

Economic evaluations of this therapy for the management of spasticity have reported incremental cost-effectiveness ratios within the UK willingness to pay threshold.[66–68] NHS England recommends the use of intrathecal baclofen for the treatment of chronic, severe, diffuse spasticity and/or dystonia of spinal or cerebral origin,[69] and IDDS for the management of severe cancer pain.[70]

Summary. The working party considers that ITDD is a cost-effective method for the management of pain and spasticity. The cost per quality adjusted life year is within the NICE willingness to pay threshold.

Therapeutic context

ITDD should be delivered in a multiprofessional context appropriate for the indication, respecting local organisational arrangements and relationships, and in partnership with the patient's primary carers. There should be an 'implantation team' which comprises the implanter, typically a pain specialist or neurosurgeon (if not a neurosurgeon there should be access to a neurosurgeon to deal with possible complications), clinical nurse specialists, pharmacists, psychologists and physiotherapists as appropriate. The implantation team will work with the patient's primary care team and with the team with responsibility for the primary condition; for CNMP this will be most commonly the department of pain medicine, for cancer pain, the palliative medicine team and for spasticity, the spinal injury or the neurological rehabilitation services. It is recognised that the management of each condition is highly specialised. All professionals have a role in assessment, choice of therapy, ongoing management, and assessment of response. Early attention should be given to the familiarisation of perioperative and ward staff with the technique.

Patients who have intrathecal implants require ongoing resources including programming, prescription adjustments, refills, monitoring of effectiveness and progression in disease, and surgery for maintenance such as pump replacements and complications. These resources must be planned and funded appropriately. Dedicated refill sessions are recommended, conducted by suitably trained and competent clinical nurse specialists or doctors in dedicated clean facilities with full support. The feasibility of conducting pump refills at the patient's home has been evaluated in a pilot study.[71] All procedures conducted during the pilot were successfully performed with complete patient satisfaction and with 95% of patients and physicians/nurses feeling

safe during the procedure. Tele-ultrasound was used as a post-refill verification. The possibility of pump refills at the patient's home may improve access to ITDD, particularly for patients with limited ability to travel to bigger centres for pump refills. As complications are potentially life threatening, arrangements must be in place for 24-h medical cover. Those undertaking refill procedures should be familiar with the technique and aware of the importance and significance of neurological symptoms and signs, and failure of pain relief. It is advisable to keep records of new symptoms, pain and spasticity scores where appropriate, expected and actual reservoir volumes and any discrepancies observed.

There should be appropriate training and expertise. There is increasing evidence across a range of neurosurgical procedures and conditions that improved outcomes are achieved in units with high case volumes and which provide a comprehensive range of therapies.[72–74] All those involved in implantation procedures must undergo appropriate training. It is important, especially for those with low caseloads (see section Patient selection / Pain associated with cancer), to develop and be involved with networks of clinicians practising ITDD. A mentoring system is recommended for support, advice and sharing of practical detail such as dosing and dose conversions.

Drugs and drug mixtures for intrathecal use should be prepared in appropriate sterile conditions, be preservative free and be compatible with the infusion device where feasible within the clinical context of the therapy. Stability and compatibility of admixtures must be addressed (see section Drugs and their side effects).

Guidance must be followed for the use of unlicensed drugs. Some preparations which are currently used do not have product licences for ITDD. The British Pain Society's 'The use of drugs beyond licence in palliative care and pain management' guidelines provide useful general advice.[75]

Safety is of prime importance. Extreme vigilance must be given to all aspects of patient and medication safety, particularly the prevention of the inadvertent administration of drugs by the wrong route. Design of systems and equipment selection to protect against this error should be encouraged. Patients' engagement in checking the route should be encouraged.

Education of the primary care team and the patient's family must be provided. Primary and secondary care staff should be aware of the nature and initial management of complications. Links with implant manufacturers and distributors are important for ongoing support and education.

Links should be established for advice from primary healthcare, rehabilitation medicine and microbiology, and with neurosurgery, radiology and critical care departments to deal with potential complications.

The patient should be fully informed of the benefits and risks of the treatment. Appropriate informed consent should be taken. Written patient information sheet should be available (Appendix 1).

Adequate records must be kept. It is the responsibility of the implanter to keep adequate records of the implantation procedure and device. The patient should carry information indicating the make and model of any device, drugs within the pump and the current or last prescribed dose.

Plans for long-term care must be considered. If patients move away from the centre where originally implanted, a mechanism needs to be in place to allow for a smooth and timely transfer of care. Regular upload of information to the national neuromodulation database should facilitate this.

Patient selection

For all indications, patient selection is extremely important and should comprise a comprehensive, multiprofessional assessment of symptoms, disease, psychological and social factors, current and previous treatments and other treatment options. ITDD can be used adjunctively and concurrently with other modes of pain management. The referral of complex, uncontrolled pain to centres able to offer a wide range of pain treatment modalities, including ITDD, should be encouraged.

CNMP

Key indications for ITDD are nociceptive pain, mixed aetiology cases of nociceptive and neuropathic pain, and neuropathic pain that has failed to respond to other management techniques including an adequate trial of spinal cord stimulation.

Examples of diagnostic groups appropriate for ITDD are patients with severe disabling pain who have inadequate symptom relief and/or drug toxicity despite appropriate intervention from a multi-disciplinary pain management team, such as:

- Patients with back and/or leg pain related to spinal disease that has neither responded favourably to spinal surgery nor spinal cord stimulation or where surgery or spinal cord stimulation were unfeasible or contraindicated;[17,76–79]
- Patients with complex regional pain syndrome associated with dystonia and/or who have failed an adequate trial of neurostimulation;[31,80]
- Patients with multiple spinal fractures secondary to osteoporosis;[81]
- Patients with neuropathic pain secondary to preganglionic nerve injury such as brachial plexus

avulsion or post cauda equina syndrome where spinal cord stimulation has failed to achieve pain relief or is deemed to be inappropriate;[82]
- Patients with chronic neuropathic visceral pain such as chronic pancreatitis or multiply operated abdomen who have been fully assessed by multidisciplinary team.[83]

Psychological assessment. For CNMP, it is strongly recommended that patients have a comprehensive psychological assessment to: (i) assess possible concurrent psychopathology (e.g. severe affective disorder, body dysmorphia and somatisation) that might impede successful outcome following implantation; and (ii) to consider what additional individualised preparation might be advisable for the patient.[84]

Cognitive behavioural therapy should not be excluded as a subsequent treatment option. It may ensure that the reduction in pain severity expected as a result of the ITDD system is capitalised upon by the development of reduced pain related behaviour and increased activity in a range of adaptive behaviours.

Trials of ITDD. There is little evidence surrounding selection trial conduct for ITDD. A single randomised controlled trial comparing intrathecal bolus to epidural infusion trials of intrathecal therapy found bolus trials to be equally safe but less costly when compared to epidural infusion trials, the study was, however, not powered to assess the ability of the trial procedure to predict long-term outcomes of the therapy.[85] A retrospective study of 86 patients implanted with ITDD for CNMP concluded that the responsiveness to an intrathecal narcotic during a trial, along with the diagnosis at the time of implantation, and the patient's age and gender can predict long-term intrathecal opioid requirements in ITDD therapy in CNMP.[86] A further retrospective review of 62 failed back surgery syndrome (FBSS) now termed persistent spinal pain syndrome type 2 (PSPS-T2) were trialled with a combination of hydromorphone and bupivacaine with a temporary externalised IT catheter of whom 54 had a successful trial.[87] The authors observed significant positive improvements in pain intensity following ITDD implant as well as significant positive correlations between pretrial oral opioid intake and end of trial hydromorphone dose and hydromorphone dose escalation at 12 and 24 months. There is to date no clear prospective study linking outcome of selection trials to long-term outcomes of the ITDD therapy in either intrathecal analgesia or baclofen use for spasticity. Where infusion trials are performed, an attempt should be made to mimic the ultimate therapy conditions in infusion rate and drug concentration. This may be more predictive of ITDD outcomes.

Conclusion. In the opinion of the working group, for this patient population, use of ITDD must be reserved for those patients with a clear medical diagnosis, positive psychological assessment and adequate information about the long-term efficacy and risks of the therapy. Trials are generally but not universally recommended. Neither bolus nor infusion trials can successfully predict long-term outcomes.

Pain associated with cancer

Pain can be managed in the majority of patients with cancer by following the WHO guidelines.[88–90] However, 10%–20% will require more intensive measures to manage pain. In a prospective study of 2118 patients with pain associated with cancer managed by the WHO guidelines, 8% required nerve blocks, 3% neurolytic blocks and 3% spinal analgesia (epidural/intrathecal).[89] The true incidence of patients requiring interventional analgesic techniques remains unknown because of varying inclusion criteria in different centres. The WHO guidelines, while appropriate from a global perspective, have not taken into consideration the increased cancer survival nor the long-term consequences of chronic systemic opioid therapy.[91] An evidence-based medicine review classified ITDD amongst the treatments that must be used for cancer-related pain.[92]

The principal indication for using ITDD in patients with pain secondary to cancer is failure of conventional routes of analgesic administration to achieve satisfactory analgesia despite escalating doses of strong opioids, and/or dose limiting side effects.[93–95] A trial and psychological assessment are not mandatory for cancer-related pain but should be considered depending on the clinical circumstances or where there is uncertainty about the response to a class or mixture of IT drugs.[91] The malignancy must be fully investigated with appropriate imaging techniques prior to a decision to undertake ITDD.

An appropriate route of delivery must be chosen. Historically, the epidural route has been the more commonly used route for continuous neuraxial drug delivery in pain associated with cancer. However, there are reports of improved pain management and fewer complications with the intrathecal route.[96–98] Additionally, if an externalised system is being used, the lower dose and volume requirements of the intrathecal route allow for longer intervals between syringe changes.[97] Similar infection rates have been reported with intrathecal or epidural administration[99] but there is evidence that intrathecal catheters are safer when they need to be in place for more than 3 weeks.[100,101]

Neurolytic or neuroablative interventions may be appropriate alternative interventions.

Despite the recommendation for the use of ITDD for patients with cancer pain, there is a substantial gap between the number of patients potentially eligible to receive this intervention and the actual provision of ITDD in England.[102] In circumstances where the referral of a cancer patient requiring urgent treatment to a fully resourced implanting centre is impractical or where ongoing follow up at that centre may prove impractical, ITDD can still be undertaken by informed agreement between clinicians and patient.

Spasticity

Either a bolus or infusion trial of intrathecal baclofen can be used to establish effectiveness. This should include appropriate assessment of the effect on function and may confirm predetermined goals. Most commonly a bolus test dose is administered via a lumbar puncture. An infusion trial via an indwelling lumbar catheter can offer a fuller assessment of the effect on function but requires a longer hospital inpatient stay and careful monitoring. There is no clear evidence that a bolus or infusion test is superior.

Types of systems

Consideration must be given to the suitability of individual systems for use with selected drugs.

Percutaneous catheter

Tunnelled or not tunnelled used with an external pump. These systems are easy to place and are suitable for patients with limited life expectancy. Percutaneous catheters require frequent monitoring for infection and migration. The technique restricts patients' mobility. Infusion devices that are not recommended to deliver intrathecal therapy should not be used.

Totally implanted catheter with a subcutaneous injection port connected to an external pump

These systems are suitable for patients with limited life expectancy[97] and are also used as a method of conducting a prolonged trial to determine suitability for a fully implanted intrathecal system. The system requires a multi professional infrastructure and close monitoring for infection. The technique restricts patients' mobility.

Fully implanted fixed rate intrathecal drug delivery systems

These systems are no longer available in the UK although some historical systems may remain in use. They are suitable for long-term use. Mobility and functional activity are not particularly adversely affected by these systems. Fixed rate delivery systems lack flexibility of prescription delivery; dosage alteration requires that the drug solution has to be changed and therefore this requires an additional procedure. These systems may have a larger reservoir volume so larger volumes can be delivered or there can be longer intervals between refills. The availability of fixed rate delivery systems is limited in the UK. Regular follow up for refilling is required.

In cases of suspected or actual medication overdose or implant malfunction the pump's drug reservoir and catheter dead space must be emptied. As the system is not power source dependent, it should last for the lifetime of the patient.

Fully implanted programmable intrathecal drug delivery systems

The implanter of these systems is required to have surgical skills or support from a surgeon and the technique should be undertaken in a specialised centre with a full multi professional infrastructure. Programmable devices provide a flexibility of prescription administration that allows for easy dose alteration without invasive intervention and have facilities for bolus and patient activated bolus programmes. Mobility and functional activity are not particularly adversely affected by these systems.

In cases of suspected or actual medication overdose or implant malfunction the pump can be deactivated without having to empty the drug reservoir. Peristaltic pumps can be damaged by complete device halt for more than a few hours. Other drive mechanisms can be stopped for any duration with no effect on the drive mechanism.

The programmable system is battery driven or controlled and battery life varies typically from 7 to 10 years. Regular attendance for refilling is required.

Patients with a limited life expectancy may be served by having an implanted programmable pump with PCA facility that allows for frequent prescription alteration with minimal invasive intervention. The programmable pumps allow drug doses to be changed as the disease progresses and/or the patient develops tolerance to opioids.

Consensus is that fully implantable systems are underused in cancer patients.

Procedure and aftercare

Preoperative preparation

Following selection for the technique, patients must be also investigated for fitness to undergo surgery and anaesthesia. In extreme circumstances this may affect the decision to implant.

Refill intervals have to be planned with regard to the stability of the chosen drug in solution as well as the concentration and dose of the drugs administered. The stability of different drug combinations used in ITDD has been reported.[103–105] Initial intrathecal dosage should not exceed manufacturers recommendations. Titration during the first weeks of therapy should be carried out with care and due regard to the balance of side effects versus benefits of an increased dosage.

Although infections are rare, staphylococcus *aureus* is the commonest organism to infect ITDD systems. *Staphylococcus epidermidis* infections can occur as a complication of refills. Methicillin resistant staphylococcus *aureus* (MRSA) screening programmes must be based on local decision guided by the Infection Control team who have knowledge of the local epidemiology.[106] For cancer patients the risk of surgical site infection may be increased due to factors that may alter the immune status, such as recent corticosteroid, chemotherapy or radiotherapy near the surgical site. The identification and mitigation of such risk may prevent infection.[107]

When drugs are to be used intrathecally, their systemic use will need to be discontinued or dose reduced preoperatively. Management of potential withdrawal effects or overdose should be planned and approached with care.

The proposed position of the pump reservoir should be agreed preoperatively between the patient and operator, taking clothes, belts, stomas, and bony prominences into consideration. Lower reservoir size pumps should be considered for smaller patients.

With consultation, anticoagulant and antiplatelet therapy should be stopped for the procedure to take place. If coagulopathy is suspected clotting should be checked.[108]

Baseline endocrine function should be measured by serum testosterone, luteinising hormone (LH) and follicle stimulating hormone (FSH) levels in men and oestradiol, progesterone, LH and FSH levels in women. The hypothalamic-pituitary-gonadal function should be monitored annually.[109,110]

ITDD patients diagnosed with hypogonadotropic hypogonadism should have routine assessment of bone mineral density (BMD) levels.[111,112] Appropriate follow-up should be provided based on the DEXA scan results.

Theatre procedure

The theatre environment should be suitable for implant surgery of any type. A theatre team and X-ray screening facilities should be available. A study in a population of cancer patients showed tunnelling, external fixation and the use of filters to reduce the risk of infection for percutaneous catheters used with an external pump.[113] Details of operative technique can be found elsewhere.[114]

There is little published evidence regarding the use of antibiotic prophylaxis in the ITDD area but extrapolation of evidence from other implanted material areas justifies the use of a preoperative large single dose of antibiotic prophylaxis.[115–117] Until such specific advice emerges it is best to follow local policy on use of peri-operative prophylactic antibiotics and medical device implantation. The consequences of infection justify detailed audit of current practice and outcomes, and research to provide evidence-based guidelines at a later date.

Inpatient management

Generic postoperative care principles apply, and aftercare should be delivered on a ward where nurses have trained and developed skills in the technique of ITDD, work according to local protocols and have appropriate medical support and equipment.

The patient should not be cared for on a ward where there is a known potential for infection transmission, for example, MRSA and VRE.

Mobilisation should start as soon as appropriate.

Discharge and ongoing care

Adequate arrangements for ongoing care should be in place to include programme changes and refill attendances. Refill intervals must not be open ended; the stability of the drug is an important consideration and determines the interval. Contact details of the local care team must be provided and arrangements for out of hour care clarified before discharge.

Additional considerations

Some ITDD systems may be at risk of significant damage and malfunction from MRI scanners. Advice should be taken from local scanning departments; all should have access to guidelines on MRI use with ITDD systems. Pump manufacturer guidance should be sought and will vary according to pump type and model, field strength of the magnet, sequences to be used and body part to be imaged, specifically whether

near the implant and whether local coils will be used. For patients with programmable devices, the pump specific manufacturer guidance should be followed in consultation with the local radiology department.

Scanners in airports and shops should be avoided; a card is provided to patients for this purpose. Advice should be taken from the implanting clinician before deep sea diving.

Therapeutic short-wave diathermy and ultrasound should not be used within 30 cm of the pump or catheter as it may lead to pump overheating and over infusion. Surgical electrocautery, Magneto-encephalography (MEG), Positron emission tomography (PET) scans and CT scans are compatible with modern programmable devices.

ITDD pumps should be removed after death if the patient is to be cremated.

In all the above and other instances of ITDD/other device or environment interaction clinicians should routinely refer to the specific device manufacturer guidance. Clinicians should note that such guidance is device specific.

Drugs and their side effects

Drugs may be used in combination to maximise analgesic effect and to minimise side effects.

Intrathecal opioids

Preservative free morphine is considered the 'gold standard' because of it its stability, receptor affinity and extensive experience of using the drug by this route.[118]

Hydromorphone is about five times more potent than morphine. It is used when there is intolerance to intrathecal morphine. The side effect profile of hydromorphone is equivalent to or better than that of morphine.[119] A retrospective comparison of patients treated with a combination of hydromorphone/bupivacaine (n = 30) to fentanyl/bupivacaine (n = 28) with 2-year follow-up observed similar levels of pain relief but a lower rate of opioid escalation in the fentanyl group.[120] The lack of availability of higher concentrations of fentanyl in the UK limits its usefulness in intrathecal therapy.

Di-acetyl morphine (diamorphine) is used in the UK. It is highly soluble in saline, bupivacaine and/or clonidine, which makes it attractive to use in an intrathecal drug admixture. Di-acetyl morphine decays to mono-acetyl morphine in implanted Synchromed pumps with half-life of 50 days.[121] Mono-acetyl morphine decays to morphine with maxima estimated at 125 days.[121] The same study concluded that di-acetyl morphine and its breakdown products provide similar analgesia to morphine alone when administered by ITDD for a period of at least 10 weeks and may be a useful alternative when a more soluble agent is favoured.

Following two case reports of precipitation of diamorphine in the Synchromed pump leading to malfunction of the pump, a consensus of pain consultants in the UK recommended that it is not advisable to use diamorphine in a newly implanted programmable Synchromed pump and the patients with diamorphine in their Synchromed pump should be changed to an alternative medication.[122] Diamorphine can be used in constant flow pumps where its high solubility is valuable. The compatibility of diamorphine with other programmable non-peristaltic ITDD devices remains to be established.

Centrally mediated side effects of intrathecal opioids include late respiratory depression,[123] pruritis, nausea, vomiting, urinary retention, sedation, constipation, oedema, weight gain, excessive perspiration, memory or mood changes and headache. Acute side effects such as nausea, vomiting, dizziness or itching are more common after commencement of the therapy and usually resolve with standard medical management during the initial 3 months.[124]

Endocrine effects include hypogonadotrophic hypogonadism, loss of libido and hypocortisism.[109] This side effect is highly prevalent,[109,110] however, hypogonadism symptoms are often denied by the patient and ignored by the physician.[125] Some patients may attribute the signs and symptoms of hypogonadism such as decreased libido, tiredness, loss of muscle mass and strength, among others to the chronic pain and its related conditions, rather than the intraspinal medication.[126,127] The hypothalamic-pituitary-gonadal axis should be routinely monitored and adequate treatment provided as undiagnosed hypogonadism may lead to low bone mineral density (BMD) levels in ITDD patients.[111] BMD can be normalised and maintained within the normal range in men with either primary or secondary hypogonadism by continuous, long-term hormonal replacement therapy.[128] Testosterone supplementation may correct the adverse effects of intrathecal opioids on testosterone levels and BMD.[112]

Intrathecal catheter tip inflammatory masses are a rare but serious side-effect with potential for neurologic morbidity if not recognised and treated appropriately. The rate of diagnosis of intrathecal granulomas in a UK centre was 7%, the equivalent to 0.009 events per patient year.[129] Granulomas are found between the spinal cord and the dura and occur mostly in the thoracic area. No association have been found between catheter tip location and development of these masses,

possibly because most implanters position the catheter tip at the thoracic level.[130] Subcutaneous injection of some, but not all opioids, induced mast cell degranulation, suggesting this may be a useful screen for potential granuloma formation with intrathecal infusion[131] although mast cell degranulation is not opioid receptor mediated it appears to be an effect of some opioid type drugs and may be implicated in granuloma formation.

Opioid induced granulomas can cause spinal cord compression, affecting motor and sensory function, and radicular pain in thoracic or lumbar regions. There is failure of analgesia as drugs are unable to reach target neural tissue. The development of a granuloma reduces the efficacy of the intrathecal medication[132] and the failure to identify the occurrence of a granuloma can lead to a diagnosis of tolerance and an increase in the rate of infusion.[133,134]

The aetiology is unknown, but it has been hypothesised that the formation of granulomas could be the result of an inflammatory reaction to the catheter,[133,134] a reaction to the trauma sustained during catheter implantation,[134] as a result of infection[135] and more commonly as a reaction to infused medication. It has also been suggested that previous spinal surgery or traumatic spinal injury may increase the risk of patients developing a granuloma.[136] When the mass is a consequence of an infection or reaction to catheter material then sometimes the granuloma can be traced along the length of the catheter.[137] As a result of infused medication, these masses have developed following administration of morphine,[138] hydromorphone,[139] diamorphine,[140] sufentanil[141] and tramadol.[142] Administration of baclofen alone has also been related to this complication.[143,144] There has been a case report associating the formation of an intrathecal granuloma with administration of fentanyl.[145] However, it is not clear if this was the only drug the patient was administered prior to identification of the mass. A retrospective comparison of patients treated with a combination of hydromorphone/bupivacaine ($n = 30$) to fentanyl/bupivacaine ($n = 28$) with 2-year follow-up observed no granulomas in either group.[120] A retrospective analysis of the records of 69 patients treated with low dose low concentration hydromorphone and followed up for an average of 33.5 ± 24 months reported an incidence of 8.7% of intrathecal granuloma with a mean time of 35 ± 7.9 months to detection of the granuloma. The authors concluded that low doses of IT opioids may not protect against granuloma formation.[146]

Animal models suggested highly concentrated opioid as the cause as infusion of saline did not result in masses. It is not clear if total daily dose or concentration of morphine is important and correlations between dose[129,147] and concentration[148] with the formation of granulomas have been described. There is a possible protective effect from clonidine added to morphine in animal models,[149] and a case series.[129] Although no association has been found, low pump flow rates may be a risk factor.[129] A randomised crossover trial observed worsening of the health state as result of higher flow rates, possibly due to a decreased effect at the receptor site.[33] Therefore, an increase in flow rate in order to prevent inflammatory masses development should take into consideration appropriate positioning of the catheter tip to obtain maximum effect at the receptor site. Animal studies have demonstrated that the cerebrospinal fluid has limited capacity to distribute intrathecally administered morphine away from the catheter tip.[150] An animal study has suggested that intermittent bolus delivery may reduce the incidence of granuloma formation.[151] A further study of 32 animals implanted with ITDD programmable devices and randomly assigned to receive infusion of 0.48 mL/day of saline or Morphine Sulphate dosing (12 mg/day at 25 mg/mL) as boluses: 1,2, 4 or 8 boluses per day given at regular intervals and flow rate of 1000 μL/h), or as a continuous infusion (25 mg/mL/20 μL/hour) found that multiple boluses reduced the rate of granuloma formation as compared to continuous infusion, suggesting bolus delivery may reduce intrathecal mass formation.[152]

Detection of a granulomatous mass in its early stages is of paramount importance. An increase in size of a granuloma occurs with the maintenance of intrathecal drug administration while it remains undetected. The appearance of clinical symptoms can be sudden. The clinical presentation of these masses is usually marked by an increase in pain while receiving the scheduled medication, which previously controlled the painful symptoms, and small increases in the intrathecal medication dose only provide temporarily relief.[153] The need for frequent increases in opioid dose escalations may be an indicator of the formation of inflammatory masses.[129] Typically, this increase is followed by slowly progressive signs and indicators of neurological deterioration including incontinence, constipation, loss of balance, sensory loss and paraparesis with a potential to culminate in functional paraplegia.[138,154] When detected early, the mass may recede using a conservative approach, which consists of replacing the medication administered with preservative-free saline[155–157] or with a different opioid[147] thus avoiding surgery. The authors report near complete resolution of the granuloma after one or

2 months. Reoccurrence of a granulomatous mass has been observed.[155,158,159] Following confirmation of the mass recession, re-initiation of intrathecal therapy should be carefully monitored to avoid recurrence of the intrathecal inflammatory mass. When surgery is elected, several alternatives are possible. Re-positioning of the catheter at a distance of about 2 to 3 cm from its prior location can be effective in preventing the growth of the mass.[154] Surgery to remove the granuloma should be considered in the presence of neurological symptoms.[155,160] This intervention is often accompanied by the removal of the catheter and occasionally, the drug reservoir, along with the mass.[138,143] There should be early involvement of neuroradiologic and neurosurgical expertise in the management of granuloma masses. The management steps should take into account the benefits as well as the risks of therapy discontinuation and spinal surgery.

Summary and recommendation. The formation of catheter tip intrathecal granulomas can be a serious consequence of mast cell degranulation associated with long-term intrathecal opioid infusions. Avoidance of high dosage and high concentration of opioids solutions has been shown to reduce the incidence of granuloma formation. Granulomas diagnosed on MR scan should be managed in consultation with neurosurgery and neuroradiology. Intrathecal granulomas causing obvious or imminent neurological deficit should be surgically excised. First time granulomas not resulting in neural compression can be managed conservatively by opioid discontinuation and or catheter relocation. In case of recurrent granulomas opioids should be discontinued or substituted indefinitely.

Intrathecal local anaesthetics

Intrathecal bupivacaine is used in the treatment of CNMP and cancer pain.[161–164] It is usually used in combination with morphine to provide better pain control for patients suffering from neuropathic pain. There is evidence that bupivacaine acts synergistically with morphine, reducing the need for increase in intrathecal morphine dose.[165–167]

Local anaesthetics can cause sensory deficits, motor impairment, signs of autonomic dysfunction and neurotoxicity. This is less likely to be a problem if continuous infusions rather than boluses are used. Clinically relevant side effects are not usually seen at bupivacaine doses of less than 15 mg per day. At higher doses, urinary retention, weakness, fatigue, somnolence and paraesthesia have been observed.

Intrathecal clonidine

Clonidine has been shown to be effective in the treatment of both cancer and neuropathic pain.[9,168] It is generally used in combination with morphine and/or bupivacaine. The admixture of clonidine and morphine acting synergistically, has been shown to be effective in patients with cancer pain and spinal cord injury.[169–171]

The most common side effects of intrathecal clonidine are hypotension, bradycardia and sedation.

Intrathecal baclofen

Intrathecal baclofen is an established treatment for relief of severe spasticity. There may be some analgesic effect.[172] Although rarely employed for chronic pain other than related to spasticity a small number of case series exist documenting its efficacy for chronic non-malignant pains such as phantom pain, failed back surgery syndrome, peripheral nerve injury and complex regional pain syndrome.[80,173]

The side effects associated with continuous infusion of baclofen are rare but include drowsiness, dizziness and constipation. Lesser degrees of overdose may cause ataxia, light-headedness and mental confusion. These effects are more likely following bolus dose compared to constant infusion.

Excessive muscle hypotonia can result in unwanted or even hazardous weakness because of reduction in the tone of respiratory muscles.

Physostigmine has been used for overdose, but a period of ventilation maybe required; the central effects should resolve within 24 h. Withdrawal may occur if the pump is not refilled properly or if there is pump or catheter malfunction and can result in rebound spasticity, motor hyperactivity, headaches, drowsiness, disorientation, hallucination, rhabdomyolysis, seizures and even death.

A degree of tolerance usually develops over a period of 6–12 months but thereafter the dose becomes stable.

Intrathecal ziconotide

Ziconotide is thought to produce its analgesic effects by blocking specific N type calcium channels found at presynaptic terminals in the dorsal horn.[174]

Side effects with ziconotide include dizziness, nausea, nystagmus, gait imbalance, confusion and urine retention. Serious but rare side effects include psychosis, suicide and rhabdomyolysis. Ziconotide should only be used by clinicians experienced in the introduction and dose escalation of the drug as well as the diagnosis and management of its side-effects.

The summary of product characteristics (SmPC) recommends that Ziconotide should be initiated at 2.4 μg/day and titrated according to analgesic response and adverse effects. Increments should be ≤2.4 μg/day up to a maximum dose of 21.6 μg/day. The minimal interval between dose increases is 24 h. For safety reasons the recommended interval is 48 h or more.[175] However, expert panels have recommended a much lower starting dosage at ≤0.5 mcg/day and a slower increase by ≤ 0.5 mcg no more than once per week.[176,177] The recommendations for a lower start dose and slower dose increase have the potential to increase the safety profile of ziconotide.

Mixtures of ziconotide with other intrathecal medications including morphine, hydromorphone, clonidine and baclofen are associated with reduction in ziconotide concentration of the order of 20% within a few weeks.[178–180]

There is no high-quality evidence to support the use of aspirin, NMDA antagonists, neostigmine, somatostatin, octreotide, midazolam, droperidol, non-steroidal anti-inflammatory preparations or adenosine by the intrathecal route.

Drug stability

Consideration must be given to stability, compatibility and sterility of intrathecal drugs (Table 1). Morphine, hydromorphone, clonidine and baclofen are stable at room and body temperature for 3 months. Bupivacaine is stable for 60 days. Refill intervals should not exceed the period of stability. There have been a number of studies published designed to address stability of admixtures.[103–105,181–185] An evaluation of the Synchromed II device showed that the accuracy and precision of intrathecal delivery were retained using unapproved drugs or admixtures under various flow modes and rates.[186] However, a pump manufacturer urgent field safety notice warned of a higher rate of device failure resulting in therapy withdrawal when the particular device (Synchromed II) is used to deliver unapproved drugs. Only Infumorph, baclofen and Ziconotide are approved for delivery in the Synchromed II device. The risk of continuing to use this device to deliver unapproved drugs/mixtures should be carefully assessed on a case-by-case basis. Patients should be fully informed of the risk and the action needed in case of therapy withdrawal.

Drug prescribing and preparation

The fear of the development of dependence, tolerance or addiction as a consequence of opioid medication contributes regularly to the stigmatisation and withholding of ITDD for CNMP.[195] A systematic review observed that the signs of opioid addiction in pain management patients corresponded to seven cases in 4884 participants, indicating a low rate of opioid addiction development (0.14%), however, these low rates of addiction should only be generalised to patients without a history of addictive/abusive behaviours.[15] Despite situations where extremely high doses of intrathecal opioids were administered, only one ITDD study has reported a possible development of opioid addiction in the form of drug seeking behaviour.[124] Recent studies have found the opioid dose to stabilise between years two and three of therapy.[195,196] The addition of intrathecal bupivacaine may contribute to stabilise the morphine dose while achieving satisfactory pain relief in the treatment of cancer pain[166,197] and non-cancer pain.[198] Younger patients (<50 years) were found to require higher intrathecal opioid doses than older patients.[199] In this study the mean age of the younger patients was 41.6 years in comparison with 64 years in the older group. The authors concluded that younger patients with CNMP could be less amenable to ITDD. However, it could be hypothesised that these differences may be related with expectations regarding the treatment and social and professional needs from younger patients which are likely to have a lesser impact on an older population.

Recommended medicines for the management of pain using ITDD devices

1st Line Therapy (single drug therapy)
Preservative free morphine or hydromorphone or ziconotide

2nd Line Therapy (opioid + adjuvant or opioid + ziconotide)
Opioid (morphine or hydromorphone) + adjuvant clonidine or bupivacaine
Opioid + Ziconotide

3rd Line Therapy (triple drug therapy)
Opioid + clonidine + bupivacaine
Opioid + ziconotide + bupivacaine

Some drugs and all drug combinations are not licensed for use in ITDD devices please refer to section Drugs and their side effects / Drug stability on the use of drugs outside license.

Role of pharmacy – general considerations

- Ensure all constituents suitable for intrathecal use (i.e. pyrogen free, preservative free) and are compatible with each other.[200]

Table 1. Drug stability (from infusion pumps at 37°C unless stated otherwise).

Study	Drug	Duration
Alvarez et al. 2004[187]	Baclofen (1 mg/mL)/Clonidine (1 mg/mL)	14 weeks
Bazin et al. 2015[188]	Morphine/Ropivacaine/Ziconotide	pH and temperature dependent; at 37°C median degradation delay of 13 days at pH ≥4.5; 3.5 days at pH <4.5 (10% loss of ziconotide)
Bianchi et al. 2008[189]	Morphine (50 mg/mL)/Bupivacaine (24 mg/mL)/ Clonidine (2 mg/mL)	90 days
	Hydromorphone (50 mg/mL)/Bupivacaine (24 mg/ mL)/Clonidine (2 mg/mL)	90 days
Classen et al. 2004[184]	Morphine (50 mg/mL)/Bupivacaine (25 mg/mL)/ Clonidine (2 mg/mL)	90 days
Dupoiron et al., 2013[103]	Ziconotide (0.1, 0.25, 0.5, and 0.75 μg/mL)/ Morphine (7.5 mg/mL)/Ropivacaine (15 μg/mL)/ Clonidine (15 μg/ml)	Ziconotide concentration 82.72% (±0.89%) after 7 days
Goucke et al. 2010[190]	Bupivacaine/Morphine (varying concentrations)	Up to 7 weeks (49 days)
	Bupivacaine/Hydromorphone (varying concentrations)	Up to 7 weeks (49 days)
Hildebrand et al. 2001[181]	Bupivacaine 7.5 mg/mL morphine	90 days
	Bupivacaine 7.5 mg/mL hydromorphone	90 days
Hildebrand et al. 2003[191]	Morphine/Clonidine	90 days
Macorigh et al. 2020[192]	Hydromorphone (15 mg/mL)/Bupivacaine (10 mg/ mL) (Stored in syringes at 37°C)	3 months
Robert et al. 2023[104]	Morphine 0.5 (mg/mL)/Ropivacaine 0.5 (mg/mL)/ Ziconotide 0.5 (μg/mL)	14 days
	Morphine 6 (mg/mL)/Ropivacaine 8.5 (mg/mL)/ Ziconotide 0.5 (μg/mL)	21 days
	Morphine 0.5 (mg/mL)/Ropivacaine 8.5 (mg/mL)/ Ziconotide 0.5 (μg/mL)	60 days
	Morphine 6 (mg/mL)/Ropivacaine 0.5 (mg/mL)/ Ziconotide 0.5 (μg/mL)	1 day
	Morphine 0.5 (mg/mL)/Ropivacaine 0.5 (mg/mL)/ Ziconotide 2 (μg/mL)	60 days
	Morphine 6 (mg/mL)/Ropivacaine 8.5 (mg/mL)/ Ziconotide 2 (μg/mL)	7 days
	Morphine 0.5 (mg/mL)/Ropivacaine 8.5 (mg/mL)/ Ziconotide 2 (μg/mL)	60 days
	Morphine 6 (mg/mL)/Ropivacaine 0.5 (mg/mL)/ Ziconotide 2 (μg/mL)	7 days
Rudich et al. 2004[193]	Hydromorphone/Clonidine	At least 35 days
Shields et al. 2005[178]	Ziconotide (25 μg/mL)/Morphine (35 mg/mL)	8 days
	Ziconotide (25 μg/mL)/Hydromorphone (35 mg/mL)	19 days
Shields et al. 2007[180]	Ziconotide (25 μg/mL)/Clonidine (2 mg/mL)	60 days
	Ziconotide (25 μg/mL)/Clonidine (2 m/mL)/ Morphine (35 mg/mL)	6 days
Shields et al. 2008[194]	Ziconotide (25 μg/mL)/Morphine (10 mg/mL)	34 days
	Ziconotide (25 μg/mL)/Morphine (20 mg/mL)	19 days
Sorrieul et al. 2023[105]	Morphine (1 mg/mL)/Clonidine (1 μg/mL)	28 days
	Morphine (10 mg/mL)/Clonidine (20 μg/mL)	28 days
	Sufentanil (3.125 μg/mL)/Clonidine (1.5 μg/mL)	7 days
	Sufentanil (40 μg/mL)/Clonidine (15 μg/mL)	28 days
Wulf et al. 1994[185]	Morphine (6.66 mg/mL)/Bupivacaine (3 mg/mL)/ Clonidine (30 μg/mL)	90 days (room temperature)

- Ensure all constituents will fit into reservoir volume.
- Water for injection may be most suitable diluent for multiple ingredient preparations to reduce common ion effect and impact on solubility.
- Check the prescribed doses are accurately measurable volumes and produce final concentrations that are programmable.
- Be aware that many drugs used in this setting maybe either unlicensed preparations or being used for off-licence indication.

Drug preparation: Drugs and mixtures used to refill ITDD pumps should ideally be prepared by hospital pharmacy aseptic services in a laminar flow preparation area.[201]

Pharmacy will ensure:

- Appropriate record keeping of the preparation steps and batch numbers of drugs used. This includes steps required to comply with CD regulations where necessary.
- Appropriate record of sterility of the mixture and duration of validity.
- Provide clear labelling identifying the patient identification, drugs used and final concentrations within the syringe with expiry date.
- Provide a double bagged securely capped syringe(s) to permit aseptic pump refilling.
- On the unusual occasion where the above is not feasible drugs should be prepared by a qualified person in a sterile environment and a record kept of the preparation steps and batch numbers of drugs used.

Maximum concentration, recommended starting and maximum daily doses of intrathecal drugs are presented in Table 2.

Complications

Prospective patients should be adequately informed of potential complications, and these should be addressed in the informed consent. Serious procedure and device related complications are rare. Minor complications are common. In a multi-centre study with cancer and non-cancer pain patients, procedure related complications occurred at a rate of 0.29 events per patient year and catheter related complications at a rate of 0.05 events per patient year.[204] The rate of complications/side-effects in a non-cancer study with a 13-years follow-up was 0.111 events per patient year.[19]

There must be clear pathways for dealing with complications, both in and out of hospital. It is recognised that it is not possible for one implanting doctor to be permanently on call; other non-implanting doctors with appropriate training in resuscitation, dealing with consequences of sudden drug withdrawal or overdose, can be responsible provided appropriate implanting doctors with pump expertise can be consulted by phone. The patient's primary care team should be aware of potential complications and have management plans.

The mortality rate following implantation was reported to be 3.89% within 1 year and superior to the 1.36% mortality rate after spinal cord stimulation implantation over the same interval.[205,206] The main cause of mortality for intrathecal drug delivery patients was respiratory depression due to opioid or central nervous system depressant drugs as a primary or contributing factor. It should, however, be considered that from the nine index cases reported by Coffey and colleagues, seven patients received an initial intrathecal opioid dose that exceeded the 0.2 to 1 mg/d dose recommended on the drug manufacturer's label; two patients had a history of prescription drug abuse or overuse, and the two patients with an initial intrathecal

Table 2. Intrathecal drugs and their recommended concentration and doses.[202]

Drug	Maximum concentration	Recommended starting dose	Maximum daily dose
Morphine	20 mg/mL	0.10–0.5 mg/day	15 mg/day
Hydromorphone	15 mg/mL	0.01–0.15 mg/day	10 mg/day
Fentanyl	10 mg/mL	25–75 mcg/day	1000 mcg/day
Bupivacaine	30 mg/mL	0.5–2 mg/day	15–20 mg/day[a]
Clonidine	1000 mcg/mL	20–100 mcg/day	600 mcg/day
Ziconotide	100 mcg/mL	0.5 mcg/day 2.4 mcg/day[b]	21.6 mcg/day[b]
Baclofen	3000 mcg/mL	50–100 mcg/day	1500 mcg/day

Adapted from the Polyanalgesic Appropriateness Consensus Conference (PACC) 2017 [202] and 2024.[203]
[a]May be exceeded in end-of-life care.
[b]Summary of Product characteristics recommendation. Note expert panel recommendations of much lower starting dose.

opioid dose within the suggested range were obese, which may contribute to decreased respiratory reserve.

Neurological deficits can occur from the procedure and from inflammatory mass development at catheter tip (see section Drugs and their side effects / Intrathecal opioids). Guidelines should be in place to permit rapid access to neuroradiological expertise and neurosurgical treatment if either is suspected. There are reports of neurotoxicity following intrathecal infusions of local anaesthetics. Several drugs have demonstrated neurotoxicity and except in special cases, are not recommended for intrathecal use.[207] There are also reports of permanent neurological damage following intrathecal local anaesthetic administration.[208]

Possible infections include meningitis[209] epidural abscess pump pocket infection or pump reservoir infection.[210] The rate of meningitis reported by studies ranged from 2.3% to 15.4% and for wound infections from 4.2% to 8.8%.[211] When considering only non-cancer pain studies, the percentage of patients with meningitis ranged from 0% to 4% and for wound infections, from 0% to 22%.[13] A large retrospective review of 154 patients implanted with ITDD identified 19 (8.71%) infections of which, 14 (6.4%) were surgical site infections.[212] Methicillin-sensitive *Staphylococcus aureus* was the most commonly isolated bacteria in this group. Meningitis was identified in 5 (2.3%) patients and was always preceded by deep surgical site infections. Median time to meningitis development was 2.2 months, after ITDD implant. Pump removal with i.v. antibiotics were the treatment of choice.

Cerebrospinal fluid leakage may result in a local hygroma or post-dural puncture headaches.[97] Post-dural puncture headache is usually self-limiting to within days.

Device-related complications include catheter kinking, disconnection, dislodgement or pump failure, programme error and overfill or incorrect refill. Catheter dye studies should be performed in cases where a catheter blockage or leak is suspected. Catheter aspiration should be ensured before injecting the dye.

Medtronic has issued a notice on the use of unapproved drugs with Synchromed II implantable infusion pump. According to this field safety notice the use of unapproved drugs and drug formulations can lead to an increased failure rate of the SynchroMed II pump include: compounded drugs, including some formulations of baclofen and morphine; admixtures for severe spasticity therapy containing baclofen with clonidine, and baclofen mixed with other drugs; admixtures for chronic pain therapy containing fentanyl and/or sufentanil, bupivacaine, clonidine, hydromorphone, morphine, and baclofen. The risks and benefits of the use of these drugs should be considered and discussed with patients on an individual basis.

Troublesome problems can occur with the pump pocket or the scar (e.g. the pump moving, the scar being thinned from within and the pump being uncomfortable).

In patients with cancer, neurological complications may occur as a result of tumour progression, vertebral collapse or obstruction of vascular supply, but may also be precipitated by bleeding or CSF leakage caused by the procedure. Unexpected paraparesis within 48 h after dural puncture occurred in five out of a series of 201 patients.[213]

In cancer, pain analgesic failure rates are high, about 30%[214] and complication rates about 45%.[12] A high proportion of patients who report failure or poor outcome with this technique will have epidural metastases or spinal stenosis.[213]

Recommendations for further research

ITDD is a therapy of last resort, as such research in the context of ITDD has proven challenging. RCTs conducted in CNMP observed challenges with recruitment and high rates of attrition both in the intervention and control arms. Instead of the usual 1:1 randomisation ratio, future RCTs should consider 1.5:1 or 2:1 ratio, therefore potential participants would have an increased chance of receiving the ITDD intervention. Inclusion of an option to crossover may also result in increases in trial retention.

Evaluation of survival benefits with ITDD could potentially be evaluated through matched-control studies and using data collected through registries. As mentioned in the NHS England Clinical Commissioning Policy document, the National Neuromodulation Registry (NNR) is available for the systematic collection of patient and device data on demography, disease severity and outcomes for all patients implanted with ITDD. Data collection through the NNR can provide a valuable resource to gather large amounts of data that may prove essential to facilitate access ITDD in populations with severe refractory pain and spasticity. Data collected through the NNR or evaluated with access to other existing registries may also allow to address multiple research questions including whether early access to ITTD in cancer-related pain is associated with extended life expectancy.

Guidelines including this one recommend placing the catheter tip above the level of pain. Such recommendations are derived from pre-clinical studies and computer modelling. Clinical studies of the same topic have returned inconclusive evidence. Further research on catheter tip positioning and drug diffusion in the spinal fluid is recommended.

Evidence for the use of ITDD in children and adolescents with cancer-related pain is limited to seven patients and further research is warranted to evaluate potential improvements in pain intensity, life expectancy, functional outcomes and device or medication related complications and side-effects in this patient population.

In order to improve access to ITDD, it is important to identify potential barriers and facilitators to treatment access and develop interdisciplinary pathways to facilitate patients to be offered this intervention and receive the required care. A potential barrier to access is a lack of awareness of ITDD and what patients may be suitable to receive this intervention.

The appropriate selection of adult and paediatric patients for ITDD for spasticity, cancer and chronic non-cancer pain needs to be better standardised for referrers, pump carers and implanters. This will improve awareness and help develop a network of care. A similar exercise was done for spinal cord stimulation using an expert consensus panel, literature evidence and RAND/UCLA methodology.

Conclusions

The technique and knowledge of the long-term effectiveness and safety of ITDD continues to evolve. New drugs being investigated for use via the intrathecal route may provide further treatment options for CNMP, cancer pain and spasticity populations. Future technology advances should strive to improve compatibility of ITDD systems with currently unapproved drugs and admixtures. Patient access to ITDD in England and Ireland needs to be improved and referral pathways strengthened. Recent evidence continues to support ITDD as an option for the management of CNMP, cancer pain and spasticity.

Declaration of conflicting interests

Sam Eldabe has received departmental funding from Medtronic outside the current work. He has received consulting fees from Medtronic and his department has received research funding from Esteve Pharmaceuticals, all outside the current work. Rui Duarte has received consulting fees from Medtronic and Esteve Pharmaceuticals outside the current work. He is an employee of Saluda Medical. Paul Farquhar-Smith has received consulting fees and remuneration for educational support from Grunenthal and consulting fees from Oxford Cannabinoid Technologies outside the current work. Somnath Bagchi is a member of the advisory board of Medtronic and received travel grants from Esteve and Boston Scientific. Lis Farquhar has received a travel grant from Esteve and Medtronic. No other conflicts were declared.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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References

1. Pert CB and Synder SH. Opioid receptor: demonstration in nervous tissue. *Science* 1973; 179: 1947–1949.
2. Yaksh TL and Rudy TA. Analgesia mediated by a direct spinal action of narcotics. *Science* 1976; 192: 1357–1358.
3. Cousins MJ, Mather LE, Glynn CJ, et al. Selective spinal analgesia. *Lancet* 1979; 1: 1141–1142.
4. Behar M, Magora F, Olshwang D, et al. Epidural morphine in treatment of pain. *Lancet* 1979; 1: 527–529.
5. Wang J, Nauss LA and Thomas JE. Pain relief by intrathecally applied morphine in man. *Anesthesiology* 1979; 50: 149–151.
6. Gourlay GK, Cherry DA and Cousins MJ. Cephalad migration of morphine in CSF following lumbar epidural administration in patients with cancer pain. *Pain* 1985; 23: 317–326.
7. Dickenson AH. Recent advances in the physiology and pharmacology of pain: plasticity and its implications for clinical analgesia. *J Psychopharmacol* 1991; 5: 342–351.
8. Taylor A and McLeod G. Basic pharmacology of local anaesthetics. *BJA Educ* 2020; 20: 34–41.
9. Eisenach JC. Three novel spinal analgesics: clonidine, neostigmine, amitriptyline. *Reg Anesth* 1996; 21: 81–83.
10. Staats PS, Yearwood T, Charapata SG, et al. Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS. *JAMA* 2004; 291: 63–70.
11. Wermeling D, Drass M, Ellis D, et al. Pharmacokinetics and pharmacodynamics of intrathecal ziconotide in chronic pain patients. *J Clin Pharmacol* 2003; 43: 624–636.
12. Williams JE, Louw G and Towlerton G. Intrathecal pumps for giving opioids in chronic pain: a systematic review. *Health Technol Assess* 2000; 4(32): 1–65.
13. Turner JA, Sears JM and Loeser JD. Programmable intrathecal opioid delivery systems for chronic noncancer pain: a systematic review of effectiveness and complications. *Clin J Pain* 2007; 23(2): 180–195.
14. Patel VB, Manchikanti L, Singh V, et al. Systematic review of intrathecal infusion systems for long-term management of chronic non-cancer pain. *Pain Physician* 2009; 12(2): 345–360.

15. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev* 2010; 2010(1): CD006605.
16. Hayek SM, Deer TR, Pope JE, et al. Intrathecal therapy for cancer and non-cancer pain. *Pain Physician* 2011; 14(3): 219–248.
17. Atli A, Theodore BR, Turk DC, et al. Intrathecal opioid therapy for chronic nonmalignant pain: a retrospective cohort study with 3-year follow-up. *Pain Med* 2010; 11(7): 1010–1016.
18. Hamza M, Doleys D, Wells M, et al. Prospective study of 3-year follow-up of low-dose intrathecal opioids in the management of chronic nonmalignant pain. *Pain Med* 2012; 13(10): 1304–1313.
19. Duarte RV, Raphael JH, Sparkes E, et al. Long-term intrathecal drug administration for chronic nonmalignant pain. *J Neurosurg Anesthesiol* 2012; 24(1): 63–70.
20. Grider JS, Etscheidt MA, Harned ME, et al. Trialing and maintenance dosing using a low-dose intrathecal opioid method for chronic nonmalignant pain: a prospective 36-month study. *Neuromodulation* 2016; 19(2): 206–219.
21. Raphael JH, Duarte RV, Southall JL, et al. Randomised, double-blind controlled trial by dose reduction of implanted intrathecal morphine delivery in chronic non-cancer pain. *BMJ Open* 2013; 3(7): e003061.
22. Pope JE, Jassal N, Sayed D, et al. A post-market, randomized, controlled, prospective study evaluating intrathecal pain medication versus conventional medical management in the non-cancer, refractory, chronic pain population (PROSPER). *Expet Rev Med Dev* 2022; 19(11): 895–904.
23. Hays RD, Spritzer KL, Schalet BD, et al. PROMIS®-29 v2.0 profile physical and mental health summary scores. *Qual Life Res* 2018; 27(7): 1885–1891.
24. Chapman CR, Lipschitz DL, Angst MS, et al. Opioid pharmacotherapy for chronic non-cancer pain in the United States: a research guideline for developing an evidence-base. *J Pain* 2010; 11(9): 807–829.
25. Rauck RL, Wallace MS, Leong MS, et al. A randomized, double-blind, placebo-controlled study of intrathecal ziconotide in adults with severe chronic pain. *J Pain Symptom Manag* 2006; 31(5): 393–406.
26. Wallace MS, Charapata SG, Fisher R, et al. Intrathecal ziconotide in the treatment of chronic nonmalignant pain: a randomized, double-blind, placebo-controlled clinical trial. *Neuromodulation* 2006; 9(2): 75–86.
27. Deer TR, Kim C, Bowman R, et al. Intrathecal ziconotide and opioid combination therapy for noncancer pain: an observational study. *Pain Physician* 2009; 12(4): E291–E296.
28. Wallace MS, Kosek PS, Staats P, et al. Phase II, open-label, multicenter study of combined intrathecal morphine and ziconotide: addition of ziconotide in patients receiving intrathecal morphine for severe chronic pain. *Pain Med* 2008; 9(3): 271–281.
29. Webster LR, Fakata KL, Charapata S, et al. Open-label, multicenter study of combined intrathecal morphine and ziconotide: addition of morphine in patients receiving ziconotide for severe chronic pain. *Pain Med* 2008; 9(3): 282–290.
30. Deer T, Rauck RL, Kim P, et al. Effectiveness and safety of intrathecal ziconotide: interim analysis of the patient registry of intrathecal ziconotide management (PRIZM). *Pain Pract* 2018; 18(2): 230–238.
31. van Rijn MA, Munts AG, Marinus J, et al. Intrathecal baclofen for dystonia of complex regional pain syndrome. *Pain* 2009; 143(1-2): 41–47.
32. van der Plas AA, Marinus J, Eldabe S, et al. The lack of efficacy of different infusion rates of intrathecal baclofen in complex regional pain syndrome: a randomized, double-blind, crossover study. *Pain Med* 2011; 12(3): 459–465.
33. Perruchoud C, Eldabe S, Durrer A, et al. Effects of flow rate modifications on reported analgesia and quality of life in chronic pain patients treated with continuous intrathecal drug therapy. *Pain Med* 2011; 12(4): 571–576.
34. Eldabe S, Duarte RV, Madzinga G, et al. Comparison of the effects of intermittent boluses to simple continuous infusion on patients' global perceived effect in intrathecal therapy for pain: a randomized double-blind crossover study. *Pain Med* 2017; 18(5): 924–931.
35. Ballantyne JC and Carwood CM. Comparative efficacy of epidural, subarachnoid and intracerebroventricular opioids in patients with pain due to cancer. *Cochrane Database Syst Rev* 2005; 2005(1): CD005178.
36. Duarte R, Copley S, Nevitt S, et al. Effectiveness and safety of intrathecal drug delivery systems for the management of cancer pain: a systematic review and meta-analysis. *Neuromodulation* 2023; 26(6): 1126–1141.
37. Perruchoud C, Dupoiron D, Papi B, et al. Management of cancer-related pain with intrathecal drug delivery: a systematic review and meta-analysis of clinical studies. *Neuromodulation* 2023; 26(6): 1142–1152.
38. Ontario Health. Intrathecal drug delivery systems for cancer pain: a health technology assessment. *Ont Health Technol Assess Ser* 2024; 24(2): 161–162.
39. Smith TJ, Staats PS, Deer T, et al. Randomized clinical trial of an implantable drug delivery system compared with comprehensive medical management for refractory cancer pain: impact on pain, drug-related toxicity, and survival. *J Clin Oncol* 2002; 20(19): 4040–4049.
40. Kenfield M, Zacharias N and Abd-Elsayed A. Intrathecal drug delivery for the treatment of cancer-associated chronic pain in children. *Neuromodulation* 2023; 26(6): 1153–1163.

41. Smith TJ, Coyne PJ, Staats PS, et al. An implantable drug delivery system (IDDS) for refractory cancer pain provides sustained pain control, less drug related toxicity, and possibly better survival compared with comprehensive medical management (CMM). *Ann Oncol* 2005; 16(5): 825–833.
42. Smith TJ and Coyne PJ. Implantable drug delivery systems (IDDS) after failure of comprehensive medical management (CMM) can palliate symptoms in the most refractory cancer pain patients. *J Palliat Med* 2005; 8(4): 736–742.
43. Hamra JG and Yaksh TL. Equianalgesic doses of subcutaneous but not intrathecal morphine alter phenotypic expression of cell surface markers and mitogen-induced proliferation in rat lymphocytes. *Anesthesiology* 1996; 85(2): 355–365.
44. Staats PS, Yearwood T, Charapata SG, et al. Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS; a randomized controlled trial. *JAMA* 2004; 291(1): 63–70.
45. Alicino I, Giglio M, Manca F, et al. Intrathecal combination of ziconotide and morphine for refractory cancer pain: a rapidly acting and effective choice. *Pain* 2012; 153(1): 245–249.
46. Dupoiron D, Bore F, Lefebvre-Kuntz D, et al. Ziconotide adverse events in patients with cancer pain: a multicenter observational study of a slow titration, multidrug protocol. *Pain Physician* 2012; 15(5): 395–403.
47. Penn RD, Savoy SM, Corcos D, et al. Intrathecal baclofen for severe spinal spasticity. *N Engl J Med* 1989; 320(23): 1517–1521.
48. Penn RD. Intrathecal baclofen for spasticity of spinal origin: seven years of experience. *J Neurosurg* 1992; 77(2): 236–240.
49. Ochs G, Struppler A, Meyerson BA, et al. Intrathecal baclofen for long-term treatment of spasticity: a multicentre study. *J Neurol Neurosurg Psychiatry* 1989; 52(8): 933–939.
50. Lazorthes Y, Sallerin–Caute B, Verdie JC, et al. Chronic intrathecal baclofen administration for control of severe spasticity. *J Neurosurg* 1990; 72(3): 393–402.
51. Loubser PG, Narayan RK, Sandin KJ, et al. Continuous infusion of intrathecal baclofen: long-term effects on spasticity in spinal cord injury. *Paraplegia* 1991; 29(1): 48–64.
52. Coffey JR, Cahill D, Steers W, et al. Intrathecal baclofen for intractable spasticity of spinal origin: results of a long-term multicenter study. *J Neurosurg* 1993; 78(2): 226–232.
53. Creamer M, Cloud G, Kossmehl P, et al. Intrathecal baclofen therapy versus conventional medical management for severe poststroke spasticity: results from a multicentre, randomised, controlled, open-label trial (SISTERS). *J Neurol Neurosurg Psychiatry* 2018; 89(6): 642–650.
54. Creamer M, Cloud G, Kossmehl P, et al. Effect of intrathecal baclofen on pain and quality of life in poststroke spasticity. *Stroke* 2018; 49(9): 2129–2137.
55. de Lissovoy G, Brown RE, Halpern M, et al. Cost-effectiveness of long-term intrathecal morphine therapy for pain associated with failed back surgery syndrome. *Clin Therapeut* 1997; 19(1): 96–112.
56. Kumar K, Hunter G and Demeria DD. Treatment of chronic pain by using intrathecal drug therapy compared with conventional pain therapies: a cost-effectiveness analysis. *J Neurosurg* 2002; 97(4): 803–810.
57. Biggs SA, Duarte RV, Raphael JH, et al. Influence of a latent period in QALY analysis: pilot study of intrathecal drug delivery systems for chronic non-malignant pain. *Br J Neurosurg* 2011; 25(3): 401–406.
58. Kumar K, Rizvi S and Bishop S. Cost effectiveness of intrathecal drug therapy in management of chronic nonmalignant pain. *Clin J Pain* 2013; 29(2): 138–145.
59. Duarte RV, Lambe T, Raphael JH, et al. Intrathecal drug delivery systems for the management of chronic noncancer pain: a systematic review of economic evaluations. *Pain Pract* 2018; 18(5): 666–686.
60. Dewilde S, Verdian L and Maclaine GD. Cost-effectiveness of ziconotide in intrathecal pain management for severe chronic pain patients in the UK. *Curr Med Res Opin* 2009; 25(8): 2007–2019.
61. Lambe T, Duarte R, Eldabe R, et al. Ziconotide for the management of cancer pain: a budget impact analysis. *Neuromodulation* 2023; 26: 1226–1232.
62. Hassenbusch SJ, Paice JA, Patt RB, et al. Clinical realities and economic considerations: economics of intrathecal therapy. *J Pain Symptom Manag* 1997; 14(3): S36–S48.
63. Mueller-Schwefe G, Hassenbusch SJ and Reig E. Cost effectiveness of intrathecal therapy for pain. *Neuromodulation* 1999; 2(2): 77–87.
64. Stearns LJ, Hinnenthal JA, Hammond K, et al. Health services utilization and payments in patients with cancer pain: a comparison of intrathecal drug delivery vs. conventional medical management. *Neuromodulation* 2016; 19(2): 196–205.
65. Stearns LJ, Narang S, Albright RE, et al. Assessment of health care utilization and cost of targeted drug delivery and conventional medical management vs conventional medical management alone for patients with cancer-related pain. *JAMA Netw Open* 2019; 2(4): e191549.
66. Sampson FC, Hayward A, Evans G, et al. Functional benefits and cost/benefit analysis of continuous intrathecal baclofen infusion for the management of severe spasticity. *J Neurosurg* 2002; 96(6): 1052–1057.

67. de Lissovoy G, Matza LS, Green H, et al. Cost-effectiveness of intrathecal baclofen therapy for the treatment of severe spasticity associated with cerebral palsy. *J Child Neurol* 2007; 22(1): 49–59.
68. Bensmail D, Ward AB, Wissel J, et al. Cost-effectiveness modeling of intrathecal baclofen therapy versus other interventions for disabling spasticity. *Neurorehabilitation Neural Repair* 2009; 23(6): 546–552.
69. NHS Commissioning Board. *Clinical commissioning policy: intrathecal baclofen (ITB)*. NHSCB/D04/P/c UK: NHS Commissioning Board, 2013.
70. NHS England. *Clinical commissioning policy: intrathecal pumps for treatment of severe cancer pain*. UK: NHS England, 2015.
71. Goudman L, De Smedt A, Huygens R, et al. Hospital at home for intrathecal pump refills: a prospective effectiveness, safety and feasibility study. *J Clin Med* 2021; 10(22): 5353.
72. Barker FGII, Curry WT and Carter BS. Surgery for primary supratentorial brain tumors in the United States, 1988 to 2000: the effect of provider caseload and centralization of care. *Neuro Oncol* 2005; 7(1): 49–63.
73. Smith ER, Butler WE and Barker FG 2nd. Craniotomy for resection of pediatric brain tumors in the United States, 1988 to 2000: effects of provider caseloads and progressive centralization and specialization of care. *Neurosurgery* 2004; 54(3): 553–563.
74. Smith ER, Butler WE and Barker FG 2nd. In-hospital mortality rates after ventriculoperitoneal shunt procedures in the United States, 1998 to 2000: relation to hospital and surgeon volume of care. *J Neurosurg* 2004; 100(2): 90–97.
75. Mike B and Karen S, Association for Palliative Medicine (APM) The Pain Society. The use of drugs beyond licence in palliative care and pain management, *The British Pain Society* 2005; 16(5): 367–368.
76. Raphael JH, Southall JL, Gnanadurai TV, et al. Long-term experience with implanted intrathecal drug administration systems for failed back syndrome and chronic mechanical low back pain. *BMC Muscoskel Disord* 2002; 3(1): 17–25.
77. Raphael JH, Southall JL, Gnanadurai TV, et al. Multiple lead spinal cord stimulation for chronic mechanical low back pain: a comparative study with intrathecal opioid drug delivery. *Neuromodulation* 2004; 7(4): 260–266.
78. Ilias W, le Polain B, Buchser E, et al. Patient-controlled analgesia in chronic pain patients: experience with a new device designed to be used with implanted programmable pumps. *Pain Pract* 2008; 8: 164–170.
79. Peng PW, Fedoroff I, Jacques L, et al. Survey of the practice of spinal cord stimulators and intrathecal analgesic delivery implants for management of pain in Canada. *Pain Res Manag* 2007; 12: 281–285.
80. van Hilten BJ, van de Beek WJ, Hoff JI, et al. Intrathecal baclofen for the treatment of dystonia in patients with reflex sympathetic dystrophy. *N Engl J Med* 2000; 343(9): 625–630.
81. Shaladi A, Saltari MR, Piva B, et al. Continuous intrathecal morphine infusion in patients with vertebral fractures due to osteoporosis. *Clin J Pain* 2007; 23(6): 511–517.
82. Brose WG, Gutlove DP, Luther RR, et al. Use of intrathecal SNX-111, a novel, N-type, voltage-sensitive, calcium channel blocker, in the management of intractable brachial plexus avulsion pain. *Clin J Pain* 1997; 13(3): 256–259.
83. De Andres J, Perotti L, Palmisani S, et al. Chronic pain due to postsurgical intra- abdominal adhesions: therapeutic options. In: Kapural L (ed). *Chronic Abdominal Pain: An Evidence-Based, Comprehensive Guide to Clinical Management*. New York: Springer, 2014, pp. 77–88.
84. Doleys DM. Preparing pain patients for implantable technologies. In: Turk DC and Gatchel RJ (eds). *Psychological approaches to pain management 2002*. 2nd ed. New York: Guilford, 2002, pp. 334–348.
85. Anderson VC, Burchiel KJ and Cooke B. A prospective, randomized trial of intrathecal injection vs. epidural infusion in the selection of patients for continuous intrathecal opioid therapy. *Neuromodulation* 2003; 6(3): 142–152.
86. Dominguez E, Sahinler B, Bassam D, et al. Predictive value of intrathecal narcotic trials for long-term therapy with implantable drug administration systems in chronic non-cancer pain patients. *Pain Pract* 2002; 2(4): 315–325.
87. Galica RJ, Hayek SM, Veizi E, et al. Intrathecal trialing of continuous infusion combination therapy with hydromorphone and bupivacaine in failed back surgery patients. *Neuromodulation* 2018; 21(7): 648–654.
88. Grond S, Zech D, Schug SA, et al. Validation of World Health Organization guidelines for cancer pain relief during the last days and hours of life. *J Pain Symptom Manag* 1991; 6(7): 411–422.
89. Zech DF, Grond S, Lynch J, et al. Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. *Pain* 1995; 63(1): 65–76.
90. Stjernsward J, Colleau SM and Ventafridda V. The world health organisation cancer pain and palliative care program: past, present and future. *J Pain Symptom Manag* 1996; 12(2): 65–72.
91. Dupoiron D, Duarte R, Carvajal G, et al. Rationale and recent advances in targeted drug delivery for cancer pain: is it time to change the paradigm? *Pain Physician* 2022; 25(3): E414–E425.

92. Chapman EJ, Edwards Z, Boland JW, et al. Practice review: evidence-Based and effective management of pain in patients with advanced cancer. *Palliat Med* 2020; 34(4): 444–453.
93. Hanks GW, Coon F, Cherny N, et al. Expert working group of the research network of the European association of palliative care. Morphine and alternative opioids in cancer pain: the EAPC recommendations. *Br J Cancer* 2001; 84: 587–593.
94. Raphael J, Ahmedzai S, Hester J, et al. Cancer pain: part 1: pathophysiology; oncological, pharmacological, and psychological treatments: a perspective from the British pain society endorsed by the UK association of palliative medicine and the royal college of general practitioners. *Pain Med* 2010; 11(5): 742–764.
95. Raphael J, Hester J, Ahmedzai S, et al. Cancer pain: part 2: physical, interventional and complimentary therapies; management in the community; acute, treatment-related and complex cancer pain: a perspective from the British Pain Society endorsed by the UK Association of Palliative Medicine and the Royal College of General Practitioners. *Pain Med* 2010; 11(6): 872–896.
96. Dahm P, Nitescu P, Applegren L, et al. Efficacy and technical complications of long-term continuous intraspinal infusions of opioid and/or bupivacaine in refractory non malignant pain; a comparison between the epidural and intrathecal approach with externalized or implanted catheters and infusion pimps. *Clin J Pain* 1998; 14: 4–16.
97. Mercadante S. Problems of long-term spinal opioid treatment in advanced cancer patients. *Pain* 1999; 79: 1–13.
98. Baker L, Lee M, Regnard C, et al. Evolving spinal analgesia practice in palliative care. *Palliat Med* 2004; 18: 507–515.
99. Gestin Y, Vainio A and Pégurier AM. Long-term intrathecal infusion of morphine in the home care of patients with advanced cancer. *Acta Anaesthesiol Scand* 1997; 41: 12–17.
100. Sjoberg M, Karlsson PA, Nordborg C, et al. Neuropathologic findings after long-term intrathecal infusion of morphine and bupivacaine for pain treatment in cancer patients. *Anaesthesiology* 1992; 76(2): 173–186.
101. Penn RD, Paice JA, Gottschalk W, et al. Cancer pain relief using chronic morphine infusion. Early experience with a programmable implanted drug pump. *J Neurosurg* 1984; 61: 302–306.
102. Duarte RV, Sale A, Desai P, et al. The unmet need for intrathecal drug delivery pumps for the treatment of cancer pain in England: an assessment of the hospital episode statistics database. *Neuromodulation* 2020; 23(7): 1029–1033.
103. Dupoiron D, Richard H, Chabert-Desnot V, et al. In vitro stability of low-concentration ziconotide alone or in admixtures in intrathecal pumps. *Neuromodulation* 2014; 17(5): 472–482.
104. Robert J, Sorrieul J, Dupoiron D, et al. Physicochemical stability study of the morphine-ropivacaine-ziconotide association in implantable pumps for intrathecal administration. *Neuromodulation* 2023; 26(6): 1179–1194.
105. Sorrieul J, Robert J, Vincent L, et al. Stability of morphine sulfate-clonidine and sufentanil-clonidine mixtures. *Neuromodulation* 2023; 26(6): 1195–1207.
106. Coia JE, Duckworth GJ, Edwards DI, et al. Guidelines for the control and prevention of meticillin-resistant Staphylococcus aureus (MRSA) in healthcare facilities. *J Hosp Infect* 2006; 63: S1–S44.
107. Scanlon MM, Gazelka HM, Moeschler SM, et al. Surgical site infections in cancer patients with intrathecal drug delivery devices. *Pain Med* 2017; 18(3): 520–525.
108. Horlocker TT. Regional anaesthesia in the patient receiving antithrombic and antiplatelets therapy. *Br J Anaesth* 2011; 107: i96–i106.
109. Abs R, Verhelst J, Maeyaert J, et al. Endocrine consequences of long-term intrathecal administration of opioids. *J Clin Endocrinol Metab* 2000; 85(6): 2215–2222.
110. Duarte RV, Raphael JH, Labib M, et al. Prevalence and influence of diagnostic criteria in the assessment of hypogonadism in intrathecal opioid therapy patients. *Pain Physician* 2013; 16(1): 9–14.
111. Duarte RV, Raphael JH, Southall JL, et al. Hypogonadism and low bone mineral density in patients on long-term intrathecal opioid delivery therapy. *BMJ Open* 2013; 3(6): e002856.
112. Finch PM, Price LM, Pullan PT, et al. Effects of testosterone treatment on bone mineral density in hypogonadal men receiving intrathecal opioids. *Pain Pract* 2015; 15: 308–313.
113. DuPen SL, Peterson DG, Bogosian AC, et al. A new permanent exteriorized epidural catheter for narcotic self-administration to control cancer pain. *Cancer* 1987; 59: 986–993.
114. Grady K and Raphael J. Spinal administration. In: Rice A (ed). *Textbook of Clinical Pain Management: Chronic volume*. London: Hodder Arnold, 2008, pp. 284–291.
115. Darouiche RO. Treatment of infections associated with surgical implants. *N Engl J Med* 2004; 350(14): 1422–1429.
116. Follett KA, Boortz-Marx RL, Drake JM, et al. Prevention and management of intrathecal drug delivery and spinal cord stimulation system infections. *Anesthesiology* 2004; 100: 1582–1594.

117. Da Costa A, Kirkorian G, Cucherat M, et al. Antibiotic prophylaxis for permanent pacemaker implantation: a meta-analysis. *Circulation* 1998; 97(18): 1796–1801.
118. Paice JA, Penn RD and Shott S. Intraspinal morphine for chronic pain: a retrospective, multicenter study. *J Pain Symptom Manag* 1996; 11: 71–80.
119. Felden L, Walter C, Harder S, et al. Comparative clinical effects of hydromorphone and morphine: a meta-analysis. *Br J Anaesth* 2011; 107(3): 319–328.
120. Ade T, Roh J, Sharma G, et al. Comparative effectiveness of targeted intrathecal drug delivery using a combination of bupivacaine with either low-dose fentanyl or hydromorphone in chronic back pain patients with lumbar postlaminectomy syndrome. *Pain Med* 2020; 21(9): 1921–1928.
121. Raphael JH, Palfrey SM, Rayen A, et al. Stability and analgesic efficacy of Diacetyl Morphine (Diamorphine) compared with morphine in implanted intrathecal pumps in Vivo. *Neuromodulation* 2004; 7: 197–200.
122. Simpson KH. *Report from a meeting to consider the use of diamorhphine in totally implantable intrathecal pumps*. UK: The British Pain Society Newsletter, 2004, pp. 10–12.
123. Gregory MA, Brock-Utne JG, Bux S, et al. Morphine concentration in brain and spinal cord after subarachnoid morphine injection in baboons. *Anesth Analg* 1985; 64: 929–932.
124. Anderson VC and Burchiel KJ. A prospective study of long-term Intrathecal morphine in the management of chronic nonmalignant pain. *Neurosurgery* 1999; 44(2): 289–300.
125. Petak SM, Nankin HR, Spark RF, et al. American Association of Clinical Endocrinologists Medical Guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients - 2002 update. *Endocr Pract* 2002; 8(6): 440–456.
126. Doleys D, Dinoff B, Page L, et al. Sexual dysfunction and other side effects of intraspinal opiate use in the management of chronic non-cancer pain. *Am J Pain Manag* 1998; 8(1): 5–11.
127. Katz N and Mazer NA. The impact of opioids on the endocrine system. *Clin J Pain* 2009; 25(2): 170–175.
128. Katznelson L, Finkelstein JS, Schoenfeld DA, et al. Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. *J Clin Endocrinol Metab* 1996; 81(12): 4358–4365.
129. Duarte RV, Raphael JH, Southall JL, et al. Intrathecal inflammatory masses: is the yearly opioid dose increase an early indicator? *Neuromodulation* 2010; 13(2): 109–113.
130. Yaksh TL, Hassenbusch S, Burchiel K, et al. Inflammatory masses associated with intrathecal drug infusion: a review of preclinical evidence and human data. *Pain Med* 2002; 3(4): 300–312.
131. Yaksh TL, Allen JW, Veesart SL, et al. Role of meningeal mast cells in intrathecal morphine-evoked granuloma formation. *Anesthesiology* 2013; 118(3): 664–678.
132. Bloomfield S, Hogg J, Ortiz O, et al. Analysis of breakthrough pain in 50 patients treated with intrathecal morphine infusion therapy. Development of tolerance or infusion system malfunction. *Stereotact Funct Neurosurg* 1995; 65(1-4): 142–146.
133. Anderson SR, Orbegozo M, Racz G, et al. Intrathecal granuloma in patients receiving high-dose intrathecal morphine therapy: a report of two cases. *Pain Pract* 2001; 1(1): 61–67.
134. Bejjani GK, Karim NO and Tzortzidis F. Intrathecal granuloma after implantation of a morphine pump: case report and review of the literature. *Surg Neurol* 1997; 48(3): 288–291.
135. Lehmberg J, Scheiwe C, Spreer J, et al. Late bacterial granuloma at an intrathecal drug delivery catheter. *Acta Neurochir* 2006; 148(8): 899–901.
136. Narouze SN, Casanova J and Souzdalnitski D. Patients with a history of spine surgery or spinal injury may have a higher chance of intrathecal catheter granuloma formation. *Pain Pract* 2014; 14(1): 57–63.
137. Langsam A. A case of spinal cord compression syndrome by a fibrotic mass presenting in a patient with an intrathecal pain management pump system. *Pain* 1999; 83(1): 97–99.
138. North RB, Cutchis PN, Epstein JA, et al. Spinal cord compression complicating subarachnoid infusion of morphine: case report and laboratory experience. *Neurosurgery* 1991; 29(5): 778–784.
139. Ramsey CN, Owen RD, Witt WO, et al. Intrathecal granuloma in a patient receiving high dose hydromorphone. *Pain Physician* 2008; 11(3): 369–373.
140. Mutagi H, Chavan S, Kapur S, et al. First report of diamorphine associated intrathecal catheter-tip granuloma. *Reg Anesth Pain Med* 2007; 32(5): 67.
141. Gupta A, Martindale T and Christo PJ. Intrathecal catheter granuloma associated with continuous sufentanil infusion. *Pain Med* 2010; 11(6): 847–852.
142. De Andrés J, Tatay Vivò J, Palmisani S, et al. Intrathecal granuloma formation in a patient receiving long-term spinal infusion of tramadol. *Pain Med* 2010; 11(7): 1059–1062.
143. Deer TR, Raso LJ and Garten TG. Inflammatory mass of an intrathecal catheter in patients receiving baclofen as a sole agent: a report of two cases and a review of the identification and treatment of the complication. *Pain Med* 2007; 8(3): 259–262.
144. Murphy PM, Skouvaklis DE, Amadeo RJ, et al. Intrathecal catheter granuloma associated with isolated

baclofen infusion. *Anesth Analg* 2006; 102(3): 848–852.
145. Zacest AC, Carlson JD, Nemecek A, et al. Surgical management of spinal catheter granulomas: operative nuances and review of the surgical literature. *Neurosurgery* 2009; 65(6): 1161–1164.
146. Veizi IE, Hayek SM, Hanes M, et al. Primary hydromorphone-related intrathecal catheter tip granulomas: is there a role for dose and concentration? *Neuromodulation* 2016; 19(7): 760–769.
147. McMillan MR, Doud T and Nugent W. Catheter-associated masses in patients receiving intrathecal analgesic therapy. *Anesth Analg* 2003; 96(1): 186–190.
148. Duarte RV, Raphael JH, Southall JL, et al. Intrathecal granuloma formation as result of opioid delivery: systematic literature review of case reports and analysis against a control group. *Clin Neurol Neurosurg* 2012; 114(6): 577–584.
149. Yaksh TL, Horais KA, Tozier NA, et al. Chronically infused intrathecal morphine in dogs. *Anesthesiology* 2003; 99(1): 174–187.
150. Flack SH, Anderson CM and Bernards C. Morphine distribution in the spinal cord after chronic infusion in pigs. *Anesth Analg* 2011; 112(2): 460–464.
151. Page L, Hildebrand K, Billstrom T, et al. Effect of intrathecal intermittent boluses and morphine concentration on the incidence of inflammatory mass in a canine model. *Neuromodulation* 2013; 16(5): e94.
152. Hildebrand KR, Page LM, Billstrom TM, et al. Characterization of effect of repeated bolus or continuous intrathecal infusion of morphine on spinal mass formation in the dog. *Neuromodulation* 2019; 22(7): 790–798.
153. Langsam A. Spinal cord compression by catheter granulomas in high-dose intrathecal morphine therapy: case report. *Neurosurgery* 1999; 44(3): 689–691.
154. Deer TR, Prager J, Levy R, et al. Polyanalgesic Consensus Conference–2012: consensus on diagnosis, detection, and treatment of catheter-tip granulomas (inflammatory masses). *Neuromodulation* 2012; 15(5): 483–495.
155. Cabbell KL, Taren JA and Sagher O. Spinal cord compression by catheter granulomas in high-dose intrathecal morphine therapy: case report. *Neurosurgery* 1998; 42(5): 1176–1180.
156. Shields D, Palma C, Khoo L, et al. Extramedullary intrathecal catheter granuloma adherent to the conus medullaris presenting as cauda equina syndrome. *Anesthesiology* 2005; 102(5): 1059–1061.
157. Toombs J, Follett K, Rosenquist R, et al. Intrathecal catheter tip inflammatory mass: a failure of clonidine to protect. *Anesthesiology* 2005; 102(3): 687–690.
158. De Andrés J, Palmisani S, Villanueva Pérez VL, et al. Can an intrathecal, catheter-tip-associated inflammatory mass reoccur? *Clin J Pain* 2010b; 26(7): 631–634.
159. Hoederath P, Gautschi OP, Land M, et al. Formation of two consecutive intrathecal catheter tip granulomas within nine months. *Cent Eur Neurosurg* 2010; 71(1): 39–42.
160. Blount J, Remley K, Yue S, et al. Intrathecal granuloma complicating chronic spinal infusion of morphine. Report of three cases. *J Neurosurg* 1996; 84: 272–276.
161. Staats PS and Mitchell VD. Future directions for intrathecal therapies. *Prog Anesthesiol* 1997; 11: 367–382.
162. Berde CB, Sethna NF, Conrad LS, et al. Subarachnoid bupivacaine analgesia for seven months for a patient with a spinal cord tumor. *Anesthesiology* 1990; 72: 1094–1096.
163. Dahm P, Nitescu P, Appelgren L, et al. Continuous intrathecal infusion of opioid and bupivacaine in the treatment of refractory pain due to postherpetic neuralgia: a case report. *Neuromodulation* 1998; 1: 85–89.
164. Krames ES and Lanning RM. Intrathecal infusional analgesia for nonmalignant pain: analgesic efficacy of intrathecal opioid with or without bupivacaine. *J Pain Symptom Manag* 1993; 8: 539–548.
165. van Dongen RT, Crul BJ and van Egmond J. Intrathecal coadministration of bupivacaine diminishes morphine dose progression during long-term intrathecal infusion in cancer patients. *Clin J Pain* 1999; 15(3): 166–172.
166. Sjoberg M, Nitescu P, Appelgren L, et al. Long-term intrathecal morphine and bupivacaine in patients with refractory cancer pain. Results from a morphine:bupivacaine dose regimen of 0.5:4.75 mg/ml. *Anesthesiology (Hagerst)* 1994; 80(2): 284–297.
167. Akerman B, Arwestrom E and Post C. Local anesthetics potentiate spinal morphine antinociception. *Anesth Analg* 1988; 67(10): 943–948.
168. Eisenach JC, Du Pen S, Dubois M, et al. Epidural Clonidine analgesia for intractable cancer pain. *Pain* 1995; 61: 391–399.
169. Coombs DW, Saunders RL, Lachance D, et al. Intrathecal morphine tolerance: use of intrathecal Clonidine, DADLE, and intraventricular morphine. *Anesthesiology* 1985; 62: 358–363.
170. Coombs DW, Saunders RL, Fratkin JD, et al. Continuous intrathecal hydromorphone and Clonidine for intractable cancer pain. *J Neurosurg* 1986; 64: 890–894.
171. Siddall PJ, Gray M, Rutkowski S, et al. Intrathecal morphine and Clonidine in the management of spinal cord injury pain: a case report. *Pain* 1994; 59: 147–148.
172. Taira T, Kawamura H, Tanikawa T, et al. A new approach to control central deafferentation pain: spinal

intrathecal baclofen. *Sterotact Funct Neurosurg* 1995; 65: 101–105.
173. Zuniga RE, Schlicht CR and Abram SE. Intrathecal baclofen is analgesic in patients with chronic pain. *Anesthesiology* 2000; 92: 876–880.
174. Bowersox SS, Gadbois T, Singh T, et al. Selective N-type neuronal voltage-sensitive calcium channel blocker, SNX-111, produces spinal antinociception in rat models of acute, persistent, and neuropathic pain. *J Pharmacol Exp Therapeut* 1996; 279: 1243–1249.
175. https://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000551/WC500041929.pdf (accessed August 2023).
176. Deer T, Krames ES, Hassenbusch SJ, et al. Polyanalgesic consensus conference 2007: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. *Neuromodulation* 2007; 10(4): 300–328.
177. Matis G, De Negri P, Dupoiron D, et al. Intrathecal pain management with ziconotide: time for consensus? *Brain Behav* 2021; 11(1): e02055.
178. Shields D, Montenegro R and Ragusa M. Chemical stability of admixtures combining ziconotide with morphine or hydromorphone during simulated intrathecal administration. *Neuromodulation* 2005; 8(4): 257–263.
179. Shields D, Montenegro R and Aclan J. Chemical stability of admixtures combining ziconotide with baclofen during simulated intrathecal administration. *Neuromodulation* 2007; 10(1): 12–17.
180. Shields D and Montenegro R. Chemical stability of ziconotide-clonidine hydrochloride admixtures with and without morphine sulfate during simulated intrathecal administration. *Neuromodulation* 2007; 10(1): 6–11.
181. Hildebrand KR, Elsberry DD and Deer TR. Stability, compatibility, and safety of intrathecal bupivacaine administered chronically via an implantable delivery system. *Clin J Pain* 2001; 17: 239–244.
182. Hildebrand KR, Elsberry DE and Anderson VC. Stability and compatibility of hydromorphone in an implantable infusion system. *J Pain Symptom Manag* 2001; 22: 1045–1047.
183. Rudich Z, Peng P, Dunn E, et al. Stability of clonidine in clonidine hydromorphone mixture from implanted intrathecal infusion pumps in chronic pain patients. *J Pain Symptom Manag* 2004; 28: 599–602.
184. Classen AM, Wimbish GH and Kupiec TC. Stability of admixture containing morphine sulfate, bupivacaine hydrochloride, and clonidine hydrochloride in an implantable infusion system. *J Pain Symptom Manag* 2004; 28: 603–611.
185. Wulf H, Gleim M and Mignat C. The stability of mixtures of morphine hydrochloride, bupivacaine hydrochloride and clonidine hydrochloride in portable pump reservoirs for the management of chronic pain syndromes. *J Pain Symptom Manag* 1994; 9: 308–311.
186. Copley S, Yassa PE, Batterham AM, et al. A clinical evaluation of the accuracy of an intrathecal drug delivery device. *Neuromodulation* 2023; 26(6): 1240–1246.
187. Alvarez J-C, De Mazancourt P, Chartier-Kastler E, et al. Drug stability testing to support clinical feasibility investigations for intrathecal baclofen-clonidine admixture. *J Pain Symptom Manag* 2004; 28(3): 268–272.
188. Bazin C, Poirier A-L and Dupoiron D. Influence of pH and temperature on ziconotide stability in intrathecal analgesic admixtures in implantable pumps and syringes. *Int J Pharm* 2015; 487(1-2): 285–291.
189. Bianchi F, Ginggen A and Tardy Y. Stability and compatibility of drug mixtures in an implantable infusion system. *Anaesthesia* 2008; 63(9): 972–978.
190. Goucke CR, Dusci LJ, Van Leeuwen S, et al. Stability and tolerability of high concentrations of intrathecal bupivacaine and opioid mixtures in chronic noncancer pain: an open-label pilot study. *Pain Med* 2010; 11(11): 1612–1618.
191. Hildebrand KR, Elsberry DD and Hassenbusch SJ. Stability and compatibility of morphine-clonidine admixtures in an implantable infusion system. *J Pain Symptom Manag* 2003; 25(5): 464–471.
192. Macorigh C, Guibbert V, Casanova M, et al. Stability study of hydromorphone and bupivacaine mixture by HPLC-UV. *Eur J Hosp Pharm* 2020; 27(2): 95–99.
193. Rudich Z, Peng P, Dunn E, et al. Stability of clonidine in clonidine-hydromorphone mixture from implanted intrathecal infusion pumps in chronic pain patients. *J Pain Symptom Manag* 2004; 28(6): 599–602.
194. Shields DE, Aclan J and Szatkowski A. Chemical stability of admixtures containing ziconotide 25 mcg/mL and morphine sulfate 10 mg/mL or 20 mg/mL during simulated intrathecal administration. *Int J Pharm Compd* 2008; 12(6): 553–557.
195. Duarte RV, Raphael JH, Haque MS, et al. A predictive model for intrathecal opioid dose escalation for chronic non-cancer pain. *Pain Physician* 2012; 15(5): 363–369.
196. Hamza M, Doleys D, Wells M, et al. Prospective study of 3-year follow-up of low-dose intrathecal opioids in the management of chronic nonmalignant pain. *Pain Med* 2012; 13(10): 1304–1313.
197. van Dongen RT, Crul BJ and De Bock M. Long-term intrathecal infusion of morphine and morphine/bupivacaine mixtures in the treatment of cancer pain: a retrospective analysis of 51 cases. *Pain* 1993; 55(1): 119–123.
198. Veizi IE, Hayek SM, Narouze S, et al. Combination of intrathecal opioids with bupivacaine attenuates opioid dose escalation in chronic noncancer pain patients. *Pain Med* 2011; 12(10): 1481–1489.

199. Hayek SM, Veizi IE, Narouze SN, et al. Age-dependent intrathecal opioid escalation in chronic noncancer pain patients. *Pain Med* 2011; 12(8): 1179–1189.
200. Specialist Pharmacy Service. Choosing an injectable medicine for intrathecal administration. https://www.sps.nhs.uk/articles/choosing-an-injectable-medicine-for-intrathecal-administration/ (accessed March 2024).
201. Ghafoor VL, Epshteyn M, Carlson GH, et al. Intrathecal drug therapy for long-term pain management. *Am J Health Syst Pharm* 2007; 64(23): 2447–2461.
202. Deer TR, Pope JE, Hayek S, et al. The polyanalgesic consensus conference (PACC): recommendations on intrathecal drug infusion systems best practices and guidelines. *Neuromodulation* 2017; 20(2): 96–132.
203. Deer TR, Hayek SM, Grider JS, et al. The polyanalgesic consensus conference (PACC)®: intrathecal drug delivery guidance on safety and therapy optimization when treating chronic noncancer pain. *Neuromodulation*, 2024. in press. doi: 10.1016/j.neurom.2024.03.003.
204. Follett KA and Naumann CP. A prospective study of catheter-related complications of intrathecal drug delivery systems. *J Pain Symptom Manag* 2000; 19: 209–215.
205. Coffey RJ, Owens ML, Broste SK, et al. Mortality associated with implantation and management of intrathecal opioid drug infusion systems to treat noncancer pain. *Anesthesiology* 2009; 111(4): 881–891.
206. Coffey RJ, Owens ML, Broste SK, et al. Medical practice perspective: identification and mitigation of risk factors for mortality associated with intrathecal opioids for noncancer pain. *Pain Med* 2010; 11(7): 1001–1009.
207. Deer TR, Prager J, Levy R, et al. Polyanalgesic Consensus Conference 2012: recommendations for the management of pain by intrathecal (intraspinal) drug delivery: report of an interdisciplinary expert panel. *Neuromodulation* 2012; 15(5): 436–464.
208. Rigler ML, Drasner K, Krejcie TC, et al. Cauda equina syndrome after continuous spinal anesthesia. *Anesth Analg* 1991; 72(3): 275–281.
209. Devulder J, Ghys L, Dhondt W, et al. Spinal analgesia in terminal care; risk versus benefit. *J Pain Symptom Manag* 1994; 9: 75–81.
210. Byers K, Axlerod P, Michael S, et al. Infections complicating tunnelled intraspinal catheter systems used to treat chronic pain. *Clin Infect Dis* 1995; 21: 403–408.
211. Deer TR, Levy R, Prager J, et al. Polyanalgesic Consensus Conference–2012: recommendations to reduce morbidity and mortality in intrathecal drug delivery in the treatment of chronic pain. *Neuromodulation* 2012; 15(5): 467–482.
212. Malheiro L, Gomes A, Barbosa P, et al. Infectious complications of intrathecal drug administration systems for spasticity and chronic pain: 145 patients from a tertiary care center. *Neuromodulation* 2015; 18(5): 421–427.
213. Applegren L, Nordborg C, Sjoberg M, et al. Spinal epidural metastasis: implications for spinal analgesia to treat 'refractory' cancer pain. *J Pain Symptom Manag* 1997; 13: 25–42.
214. Chrubasik J, Chrubasik S and Martin E. Patient-controlled spinal opiate analgesia in terminal cancer. Has its time really arrived? *Drugs* 1992; 43(6): 799–804.

Appendix

Patient information leaflet

British Pain Society. Intrathecal drug delivery system for treating pain and spasms – Information for patients. December 2015 https://www.britishpainsociety.org/static/uploads/resources/files/ITDD_2015_version_patients_Final.pdf

NHS England Policies on ITDD

Intrathecal Baclofen: NHSCB/D04/P/c
https://www.england.nhs.uk/wp-content/uploads/2013/04/d04-p-c.pdf

Intrathecal pumps for treatment of severe chronic pain: NHS England D08/P/a
https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/d08pa-intrathecal-pumps-oct15.pdf

Intrathecal Pumps for Treatment of Severe Cancer Pain: NHS England: D08/P/b
https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/d08pb-intra-pumps-trtmnt.pdf