



## **British Pain Society**

Intrathecal drug delivery for the management of pain and spasticity in adults; recommendations for best clinical practice

**December 2015**

To be reviewed February 2018

Published by:  
The British Pain Society  
3rd floor  
Churchill House  
35 Red Lion Square  
London WC1R 4SG

Website: [www.britishpainsociety.org](http://www.britishpainsociety.org)

ISBN: 978-0-9935145-0-0

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# Contents

|   |   |    |
|---|---|----|
|   | Introduction and purpose  | 4  |
|   | Membership of the update working group                                | 5  |
|   | Conflict of Interest declarations                                     | 6  |
|   | Membership of the original guidance working group                     | 7  |
|   | Executive summary   | 8  |
| 1 | Scientific rationale  | 9  |
| 2 | Evidence for effectiveness  | 10 |
| 3 | Therapeutic context   | 15 |
| 4 | Patient selection   | 17 |
| 5 | Types of systems  | 21 |
| 6 | Procedure and aftercare   | 23 |
| 7 | Additional considerations   | 25 |
| 8 | Drugs and their side effects  | 26 |
| 9 | Complications   | 34 |
|   | Recommended Medicines for the management of pain using ITDD Devices * | 36 |

## Introduction and purpose

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 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 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.

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

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/MHRA recommendations as well as provide an update on the indications and complication management particularly endocrine complications and intrathecal granuloma formation

Members of the update working group used their own clinical and research experience in the subjects of ITDD. Members also conducted a thorough search of the literature and reviewed the most recent publications of the international polyanalgesic consensus conference 2012 and amended sections of the guidance where it was felt that changes in evidence or international guidance were relevant to UK practice.

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The update working group wish to express their gratitude to Dr. Karen Simpson of the *Faculty of Pain Medicine* and *The British Pain Society* for her revision of the final manuscript

## Conflict of Interest declarations

Prof Sam Eldabe has received departmental funding from Medtronic to conduct studies on intrathecal therapy; he has consulted for Medtronic but not in the area of intrathecal drug delivery.

Dr. Rui Duarte: No conflicts declared

Dr. Simon Thomson: No conflicts declared

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## 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 relating to the use of ziconotide and a supportive small randomised controlled study as well as several prospective open studies.
- For pain in patients with cancer there is randomised controlled trial evidence.
- For spasticity there are well designed open studies for effectiveness as well as evidence for cost effectiveness. Randomised controlled trials in stroke related spasticity are ongoing.
- 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 ongoing work into design and delivery 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 a 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 ITDD opioid use (e.g. tolerance, granuloma formation and hormone suppression). In this respect people with cancer with a near normal life expectancy should be counselled as with CNMP patients.

# 1 Scientific rationale

## 1.1 Use in pain associated with cancer and CNMP

- 1.1.1** 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].
- 1.1.2** 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.
- 1.1.3** Intrathecal clonidine, an  $\alpha_2$  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.
- 1.1.4** 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].

## 1.2 Use in Spasticity

Intrathecal baclofen is used in the treatment of 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  $\gamma$ -aminobutyric acid (GABA) mediated inhibition. Baclofen (a GABA agonist) restores the balance.

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## 2 Evidence for effectiveness

### 2.1 Chronic Non Malignant Pain (CNMP)

Several systematic reviews have assessed the clinical effectiveness of ITDD for the management of CNMP [1-5]. None of these systematic reviews identified randomised controlled trials 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 [4]. 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 [6-8]. The morphine dose escalation was found to significantly increase throughout the 3-year period in one of the studies [6]. The two prospective studies, observed that intrathecal morphine dose escalation stabilised between 24 and 36 months [7] and after 36 months post-implantation [8]. A prospective study of low-dose intrathecal opioids in the management of 61 chronic nonmalignant 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 [7]. Oral opioid averaged 128.9 mg of morphine equivalent/patient/day at baseline to 3.8mg at 36 months [7]. Duarte et al followed up a cohort of 20 patients with chronic non-cancer pain treated with ITDDs for an average 13 years [8]. Statistically significant improvements were observed for the following sensory and psychosocial variables: pain intensity, pain relief coping, self-efficacy, depression, quality of life, housework, mobility, sleep, and social life between baseline and 4 year data. No statistically significant changes were detected between assessments at averages of 4 and 13.5 years [8].

In the only available randomised controlled trial (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 [9]. Fifteen patients were randomised to control (n=5) or intervention (20% dose reduction n=10) and included an intention-to-treat analysis. Owing to increasing severity of pain, seven patients (in the intervention arm) withdrew from the study prematurely. The visual analogue scale (VAS) change between baseline and the last observation was smaller in the control group (median, Mdn=11) than in the intervention group (Mdn=30.5), although not statistically significant,  $Z=-1.839$ ,  $p=0.070$ ;  $r=-0.47$ . Within groups, VAS was significantly lower at baseline (Mdn=49.5) than at the last observation (Mdn=77.5) for the reduction group,  $Z=-2.805$ ,  $p=0.002$ ;  $r=-0.627$  but not for the control group ( $p=0.188$ ). These findings are based on a small sample (n=15) conducted at a single centre.

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%) [10].

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% [11] and 31% [12]. Short-term (4 to 12 weeks) observational [13] and open-label studies [14, 15] 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 [13, 14] or ziconotide [15].

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 ITB [16]. 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 ITB administration, and were followed up for 12 months to assess long-term efficacy and safety (open-label study). Thirty-six patients entered the open-label study. Intention-to-treat analysis revealed a substantial improvement in patient and assessor-rated dystonia scores, pain, disability and quality-of-life (QoL) at 12 months.

Two further double blinded 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 [17, 18]. 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 quality of life but did not result in improved pain or spasticity relief.

### **Summary:**

The working group believes that there is mounting evidence of the effectiveness of ITDD in patients with CNMP. Large scale randomised controlled trials of ITDD in CNMP have shown limited short-term efficacy of ziconotide. One small RCT supports the efficacy of intrathecal opioids in long term patients while numerous prospective studies show long term efficacy. The place of low dose ITDD opioids (micro dosing) in practice is yet to be established.

## **2.2 Pain in patients with cancer**

Evidence from a Cochrane systematic review supports the use of intrathecal opioid therapy for pain that has not been adequately controlled by systemic treatment [19]. There has been one comparator study describing superior efficacy of intrathecal drug delivery compared with conventional medical management [20]. There are numerous case reports describing the efficacy of neuraxial drug delivery in cancer patients.

Smith and colleagues in a multicentre, international, randomised controlled trial showed improved quality of life, by reason of pain control, and significantly less drug toxicity with intrathecal drug delivery compared to comprehensive medical management [20-22]. 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' [21]. Mobility and alertness among other reasons may contribute to an improvement in longevity. Laboratory evidence indicates that systemic morphine inhibits the immune system [23]. Therefore, morphine given systemically might adversely affect survival in a cancer population when compared with intrathecal analgesia.

One randomised controlled trial demonstrated the usefulness of intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS [24]. Moderate to complete pain relief was reported with an average reduction in pain scores of 53%. A prospective observational study of 20 cancer patients treated with morphine/ziconotide combination reported a mean daily visual analogue scale of pain intensity (VASPI) score at rest of  $90 \pm 7$  [25]. All had a disseminated cancer with bone metastases involving the spine. The percentage changes in VASPI mean scores from baseline to 2 days, 7 days, and 28 days were  $39 \pm 13\%$  (95% confidence interval [CI] = 13.61–64.49,  $P < .001$ ),  $51 \pm 12\%$  (95% CI = 27.56–74.56,  $P < .001$ ), and  $62 \pm 13\%$  (95% CI = 36.03–87.89%,  $P < .001$ ), respectively [25]. In a long term cohort study with malignant pain patients ( $n=77$ ) using a low starting dose and slow upward titration regimen showed a mean decrease in pain intensity of approximately 48% from baseline [26].

**Summary:**

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

**2.3 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 [27-32].

**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 wheel chair bound patients with spasticity non responsive to systemic medication.

**2.4 Cost effectiveness**

A variety of full economic evaluations have investigated the costs and benefits associated with the use of intrathecal morphine for CNMP [33-36]. 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) [35].

A cost-utility analysis for intrathecal ziconotide use in CNMP was carried out in the UK [37]. 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 £8,206-£25,405] and £44,700 [95% CI £30,541-£62,670].

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 [38,39].

Economic evaluations of this therapy for the management of spasticity have reported incremental cost-effectiveness ratios within the UK willingness to pay threshold [40-42].

NHS England recommends the use of intrathecal baclofen for the treatment of chronic, severe, diffuse spasticity and/or dystonia of spinal or cerebral origin in its policy [43].

**Summary:**

The working party believes ITDD to be a cost effective method of opioid and baclofen delivery for pain and spasticity. The cost per quality adjusted life year is within the NICE willingness to pay threshold.

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## 3 Therapeutic context

- 3.1 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.
- 3.2 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 sterile facilities with full support. As complications are potentially life threatening, arrangements must be in place for 24-hour 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.
- 3.3 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 [1-3]. All those involved in implantation procedures must undergo appropriate training. It is important, especially for those with low caseloads (see section 4.2.6), 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.
- 3.4 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 8.7).
- 3.5 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 [4].
- 3.6 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.
- 3.7 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.
- 3.8 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.

- 3.9 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).
- 3.10 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.
- 3.11 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.

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## 4 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. Intrathecal drug delivery 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.

### 4.1 CNMP

**4.1.1** 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 [1-5];
- Patients with complex regional pain syndrome associated with dystonia and/or who have failed an adequate trial of neurostimulation [6, 7];
- Patients with multiple spinal fractures secondary to osteoporosis [8];
- 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 [9];
- Patients with chronic neuropathic visceral pain such as chronic pancreatitis or multiply operated abdomen who have been fully assessed by multidisciplinary team [10].

**4.1.2 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, somatisation) that might impede successful outcome following implantation; and ii) to consider what additional individualised preparation might be advisable for the patient [11].

**4.1.3 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 capitalized upon by the development of reduced pain related behaviour and increased activity in a range of adaptive behaviours.

**4.1.4 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 [12]. 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 [13]. 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 party, for this group of patients, 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. Trials can provide useful information on ability to respond, side effects, etc.

## 4.2 Pain associated with cancer

**4.2.1 Pain can be managed in the majority of patients with cancer by following the WHO guidelines [14-16].** 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) [15]. The true incidence of patients requiring interventional analgesic techniques remains unknown because of varying inclusion criteria in different centres.

**4.2.2 The principal indication** for using intrathecal drug delivery 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 [17-19]. A trial may or may not be appropriate depending on the clinical circumstances.

**4.2.3 The malignancy must be fully investigated** with appropriate imaging techniques prior to a decision to undertake ITDD.

**4.2.4 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 [20-22]. Additionally, if an externalized system is being used, the lower dose and volume requirements of the intrathecal route allow for longer intervals between syringe changes [21]. Similar infection rates have been reported with intrathecal or epidural administration [23] but there is evidence that intrathecal catheters are safer when they need to be in place for more than three weeks [24, 25].

**4.2.5 Neurolytic or neuroablative** interventions may be appropriate alternative interventions.

- 4.2.6** ITDD currently appears to be underused in pain associated with cancer in the UK. 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.

### 4.3 Spasticity

- 4.3.1** 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. An infusion trial offers a fuller assessment of the effect on function.

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## 5 Types of systems

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

- 5.1** Percutaneous catheter (tunnelled or not tunnelled) used with an external pump.
  - 5.1.1** These systems are easy to place and are suitable for patients with limited life expectancy.
  - 5.1.2** Percutaneous catheters require frequent monitoring for infection and migration. The technique restricts patients' mobility.
  - 5.1.3** Infusion devices that are not recommended to deliver intrathecal therapy should not be used.
- 5.2** Totally implanted catheter with a subcutaneous injection port connected to an external pump.
  - 5.2.1** These systems are suitable for patients with limited life expectancy [1] and are also used as a method of conducting a prolonged trial to determine suitability for a fully implanted intrathecal system.
  - 5.2.2** The system requires a multi professional infrastructure and close monitoring for infection. The technique restricts patients' mobility.
- 5.3** Fully implanted fixed rate intrathecal drug delivery systems.
  - 5.3.1** These systems are suitable for long term use. Mobility and functional activity are not particularly adversely affected by these systems.
  - 5.3.2** The implanter is required to have surgical skills or support from a surgeon, and patients require specialised centre care with a full multi professional infrastructure.
  - 5.3.3** Fixed rate delivery systems are less expensive than variable rate delivery systems but 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 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.
  - 5.3.4** Regular follow up for refilling is required.
  - 5.3.5** In cases of suspected or actual medication overdose or implant malfunction the pump's drug reservoir and catheter dead space have to be emptied.
  - 5.3.6** As the system is not power source dependent, it should last for the lifetime of the patient.
- 5.4** Fully implanted programmable intrathecal drug delivery systems.
  - 5.4.1** 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.
  - 5.4.2** Mobility and functional activity are not particularly adversely affected by these systems.

- 5.4.3** In cases of suspected or actual medication overdose or implant malfunction the pump can be deactivated without having to empty the drugs 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.
- 5.4.4** The programmable system is battery driven or controlled and battery life varies typically from 7-10 years.
- 5.4.5** Regular attendance for refilling is required.
- 5.5** External infusion devices are used more in the management of cancer pain than fully implanted systems. The choice of system is, however, heavily influenced by cost. 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. There is a place for both constant rate devices and programmable devices; the constant rate pumps have the advantage of a larger volume reservoir, allowing larger volumes to be delivered or a longer interval between refills. 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.

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## 6 Procedure and aftercare

### 6.1 Preoperative preparation

- 6.1.1** 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.
- 6.1.2** 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. 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 vs. benefits of an increased dosage.
- 6.1.3** 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 [1].
- 6.1.4** 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.
- 6.1.5** The proposed position of the pump reservoir should be agreed preoperatively between the patient and operator, taking clothes and belts into consideration. There are a range of reservoir sizes available for smaller patients.
- 6.1.6** With consultation, anticoagulant and antiplatelet therapy should be stopped for the procedure to take place. If coagulopathy is suspected clotting should be checked [2].
- 6.1.7** 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 [3, 4].
- 6.1.8** ITDD patients diagnosed with hypogonadotropic hypogonadism should have routine assessment of bone mineral density (BMD) levels [5, 6]. Appropriate follow-up should be provided based on the DEXA scan results.

### 6.2 Theatre procedure

- 6.2.1 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 [7]. Details of operative technique can be found elsewhere [8].

- 6.2.2.** 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 [9-11]. 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.

### 6.3 Inpatient management

- 6.3.1** 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.
- 6.3.2** The patient should not be cared for on a ward where there is a known potential for infection transmission e.g MRSA and VRE.
- 6.3.3** Mobilisation should start as soon as appropriate.

### 6.4 Discharge and ongoing care

- 6.4.1** 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.

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## 7 Additional considerations

- 7.1 MRI Scans.** Some ITDD systems are 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 this. 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. Patients with fixed rate delivery systems should have both the reservoir and catheter emptied prior to the scan then be refilled once completed. However if the catheter is emptied then issues relating to potential drug withdrawal and resulting increase in pain and spasms need to be addressed. For patients with programmable devices, the pump specific manufacturer guidance should be followed in consultation with local radiology department.
- 7.2** Scanners in airports and shops should be avoided; patients are able to show a card to accommodate this.
- 7.3** Patients with fixed rate delivery systems should be advised to avoid saunas and sunbeds as the increase in heat may cause the implant to increase its rate of delivery.
- 7.4** Advice should be taken from the implanting clinician before deep sea diving.
- 7.5** Short wave diathermy should not be used within 30 cm of the pump or catheter.
- 7.6** ITDD pumps should be removed after death if the patient is to be cremated.
- 7.7** In all the above 7.1-7.6 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.

## 8. Drugs and their side effects

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

### 8.1 Intrathecal opioids

**8.1.1** Preservative free morphine is considered the 'gold standard' because of its stability, receptor affinity and extensive experience of using the drug by this route [1].

**8.1.2** 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 [2].

**8.1.3** 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 [3]. Mono-acetyl morphine decays to morphine with maxima estimated at 125 days [3]. The same study concluded that di-acetyl morphine and its breakdown products provide similar analgesia to morphine alone when administered by intrathecal pump for a period of at least ten 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 [4]. 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.

**8.1.4** Centrally mediated side effects of intrathecal opioids include late respiratory depression [5], 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 three months [2].

**8.1.5** Endocrine effects include hypogonadotrophic hypogonadism, loss of libido and hypocortisism [6]. This side effect is highly prevalent [6, 7], however, hypogonadism symptoms are often denied by the patient and ignored by the physician [8]. 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 [9, 10]. 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 [11]. 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 [12]. Findings from a recent study suggest that testosterone supplementation can correct the adverse effects of intrathecal opioids on testosterone levels and BMD [13].

**8.1.6** 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 [14]. Granulomas are found between the spinal cord and the dura and occur mostly in the thoracic area. No association has been found between catheter tip location and development of these masses, possibly because most implanters position the catheter tip at the thoracic level [15]. 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 [16] 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 [17] 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 [18, 19].

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 [18, 19], a reaction to the trauma sustained during catheter implantation [19], as a result of infection [20] and more commonly as a reaction to infused medication. Recently it has also been suggested that previous spinal surgery or traumatic spinal injury may increase the risk of patients developing a granuloma [21]. 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 [22]. As a result of infused medication, these masses have developed following administration of morphine [23], hydromorphone [24], diamorphine [25], sufentanil [26] and tramadol [27]. Administration of baclofen alone has also been related to this complication [28, 29]. There has been a case report associating the formation of an intrathecal granuloma with administration of fentanyl [30]. However it is not clear if this was the only drug the patient was administered prior to identification of the mass. Animal models suggested highly concentrated opioid as the cause and 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 [14, 31] and concentration [32] with the formation of granulomata have been described. There is a possible protective effect from clonidine added to morphine in animal models [33], and a longitudinal study [14]. Although no association has been found, low pump flow rates may be a risk factor [14]. A randomised crossover study observed worsening of the health state as result of higher flow rates, possibly due to a decreased effect at the receptor site [34]. 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 [35]. A recent animal study has suggested that intermittent bolus delivery may reduce the incidence of granuloma formation [36]. These early findings need confirmation from longitudinal studies in patients receiving bolus infusions.

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 [37]. The need for frequent increases in opioid dose escalations may be an indicator of the formation of inflammatory masses [14]. 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 [23, 38]. When detected early, the mass may recede using a conservative approach, which consists of replacing the medication administered with preservative-free saline [39-41] or with a different opioid [31] thus avoiding surgery. The authors report near complete resolution of the granuloma after one or two months. Reoccurrence of a granulomatous mass has been observed [39, 42, 43]. 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. Repositioning 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 [38]. Surgery to remove the granuloma should be considered in the presence of neurological symptoms [39, 44]. This intervention is often accompanied by the removal of the catheter and occasionally, the drug reservoir, along with the mass [23, 28]. There should be early involvement of neuroradiology and neurosurgery 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.

## **8.2 Intrathecal local anaesthetics**

- 8.2.1** Intrathecal bupivacaine is used in the treatment of CNMP and cancer pain [45-48]. 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 [49-51].
- 8.2.2** 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 15mg per day. At higher doses urinary retention, weakness, fatigue, somnolence and paraesthesia have been observed.

### 8.3 Intrathecal clonidine

**8.3.1** Clonidine has been shown to be effective in the treatment of both cancer and neuropathic pain [52, 53]. 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 [54-56].

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

### 8.4. Intrathecal baclofen

**8.4.1** Intrathecal baclofen is an established treatment for relief of severe spasticity. There may be some analgesic effect [57]. Although rarely employed for chronic pain other than related to spasticity a small number of case series exist documenting its efficacy for chronic nonmalignant pains such as phantom pain, failed back surgery syndrome, peripheral nerve injury and complex regional pain syndrome [58, 59].

**8.4.2** 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 may be required; the central effects should resolve within 24 hours. 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.

### 8.5 Intrathecal ziconotide

**8.5.1** Ziconotide is thought to produce its analgesic effects by blocking specific N type calcium channels found at presynaptic terminals in the dorsal horn [60].

**8.5.2** Side effects with ziconotide include dizziness, nausea, nystagmus, gait imbalance, confusion, and urine retention. Serious but rare side effects include psychosis, suicide, 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 hours. For safety reasons the recommended interval is 48 hours or more [61]. **However, an expert panel has recommended a much lower starting dosage at 0.5 mcg/day and a slower increase by 0.5mcg steps every week [62].**

- 8.5.3** 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 [63-65].
- 8.6** 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.
- 8.7** Consideration must be given to stability, compatibility and sterility of intrathecal drugs. Morphine, hydromorphone, clonidine and baclofen are stable at room and body temperature for three months. Bupivacaine is stable for 60 days. Refill intervals should not exceed the period of stability. In recent years there have been a number of studies published designed to address stability of admixtures. More work is needed in this area [66-70]. A recent 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.**
- 8.8** 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 [71]. A systematic review observed that the signs of opioid addiction in pain management patients corresponded to seven cases in 4,884 participants, indicating a low rate of opioid addiction development (0.14%), however these low rates of addiction should only be generalized to patients without a history of addictive/ abusive behaviours [72]. 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 [2]. Recent studies have found the opioid dose to stabilise between years 2 and 3 of therapy [71, 73]. The addition of intrathecal bupivacaine may contribute to stabilize the morphine dose while achieving satisfactory pain relief in the treatment of cancer pain [74, 75] and non-cancer pain [76]. Younger patients (<50 years) were found to require higher intrathecal opioid doses than older patients [77]. 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.

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## 9 Complications

**9.1** 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 [1]. The rate of complications / side-effects in a non-cancer study with a 13-year follow-up was 0.111 events per patient year [2].

**9.2** 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, and proficient in the use of implanted pumps can be responsible. 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 [3, 4]. 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 9 index cases reported by Coffey and colleagues, 7 patients received an initial intrathecal opioid dose that exceeded the 0.2 to 1 mg/d dose recommended on the drug manufacturer's label; 2 patients had a history of prescription drug abuse or overuse, and the 2 patients with an initial intrathecal opioid dose within the suggested range were obese, which may contribute to decreased respiratory reserve.

**9.3** Neurological deficits can occur from the procedure and from inflammatory mass development at catheter tip (see section 8.1.6). 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 [5]. There are also reports of permanent neurological damage following intrathecal local anaesthetic administration [6].

**9.4** Possible infections include meningitis [7] epidural abscess pump pocket infection or pump reservoir infection [8]. The rate of meningitis reported by studies ranged from 2.3% to 15.4% and for wound infections from 4.2% to 8.8% [9]. 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% [10].

**9.5** Cerebrospinal fluid leakage may result in a local hygroma or post-dural puncture headaches [11]. Post-dural puncture headache is usually self-limiting to within days.

**9.6** Device-related complications include catheter kinking, disconnection, dislodgement or pump failure, programme error and overflow or incorrect refill.

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.

**9.7** 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).

- 9.8** 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 hours after dural puncture occurred in 5 out of a series of 201 patients [12].
- 9.9** In cancer pain analgesic failure rates are high, about 30% [13] and complication rates about 45% [14]. A high proportion of patients who report failure or poor outcome with this technique will have epidural metastases or spinal stenosis [12].

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## 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 (Combination therapy)

### 3rd Line Therapy: (triple drug therapy)

- Opioid + clonidine + bupivacaine

| Drug          | Recommended starting dose | Recommended Maximum daily dose | Recommended maximum concentration |
|---------------|---------------------------|--------------------------------|-----------------------------------|
| Morphine      | 0.1-0.5mg/day             | 15mg/day                       | 20mg/ml                           |
| Hydromorphone | 0.02-0.5mg/day            | 10mg/day                       | 15 mg/ml                          |
| Fentanyl      | 25-75mcg/day              | No Known limit                 | 10mg/ml                           |
| Bupivacaine   | 1-4 mg/day                | 10mg/day                       | 30mg/ml                           |
| Clonidine     | 40-100mcg/day             | 40-600mcg/day                  | 1000mc/ml                         |
| Ziconotide    | 0.5-2.4mcg/day            | 19.2 mcg/day                   | 100mc/ml                          |
| Baclofen      | 25-100 mcg/ day           | 1,500mcg/day                   | 2000-3000mcg/ml                   |

Table 1. Starting doses recommended maximum daily doses and concentrations (adapted from Deer, T. R., et al. (2012). "Polyanalgesic Consensus Conference 2012: Recommendations for the Management of Pain by Intrathecal (Intraspinal) Drug Delivery: Report of an Interdisciplinary Expert Panel." *Neuromodulation* 15(5): 436-466.

- Some drugs and all drug combinations are not licensed for use in ITDD devices please refer to the BPS guidelines on the use of drugs outside license (see 8.7)

### NHS England Policies on ITDD:

Intrathecal Baclofen: NHSCB/D04/P/c

<http://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  
<http://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  
<http://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2015/10/d08pb-intra-pumps-trtmnt.pdf>



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