THE BRITISH PAIN SOCIETY

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

Prepared on behalf of the British Pain Society
in consultation with the Association for Palliative Medicine and
the Society of British Neurological Surgeons.

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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 and adequate concentrations cannot be achieved by systemic administration, or only by high systemic doses. Delivery of the drug by the intrathecal route is a means of achieving these 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 intrathecal drug delivery (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 opinion of the working group.

The recommendations are accompanied by information for patients and their carers, intended to inform and support patients in their decisions.

Executive summary

- Intrathecal drug delivery can be an effective method of pain control; it has a supportive evidence base.
- There are three major categories of application namely
    - chronic non malignant pain (CNMP)
    - cancer pain
    - spasticity
- For CNMP there is presently no randomised controlled trial evidence but supportive prospective open studies
- For cancer pain there is randomised controlled trial evidence
- For spasticity there are well designed open studies for effectiveness
- Patient selection is important, particularly when used for CNMP. It must be carried out 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.
- Adherance to best practice is essential. Uniformity of best practice should be encouraged; this does not stifle development in the use of the technique.
- Safety is paramount. The working group strongly support research and ongoing work into design safety.
- In the opinion of the working group ITDD is an underused technique in all three categories of CNMP, cancer pain and spasticity and should be made more widely available.

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Competing interests
Members of the group have registered all competing interests as follows:

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Has no competing interests.

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Has no competing interests.

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We have contacted representatives of those groups for whom we feel these recommendations have relevance.

Contents

1 Scientific rationale

1.1 Use in Cancer pain 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 phenomenom 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].

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

1.2.3 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) [8]. It has been hypothesised that clonidine also suppresses preganglionic sympathetic outflow.

1.2.4 Ziconotide is a calcium channel antagonist specific to the calcium channels found at presynaptic terminals in the dorsal horn of the spinal cord [9]. Intrathecal ziconotide is thought to produce its analgesic effects by blocking neurotransmitter release in primary nociceptive afferent fibres.

1.2 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.

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2 Evidence for effectiveness

2.1 Chronic Non Malignant Pain (CNMP)

A recent prospective controlled study, which looked at short term efficacy, shows spinal morphine to be of use in CNMP patients who respond to systemic morphine but in whom side effects have become intolerable [1]. There are more than 100 open studies (of which at least 16 have assessed pre-and post-intervention pain scores) supporting the use of intrathecal drug delivery in terms of long term pain relief and improved quality of life. Four of these scored well for quality according to the Guidelines of the University of York [2] these being Anderson et al 1999 [3], Hassenbusch et al 1996 [4], Tutak et al 1996 [5] and Winkelmuller et al 1996 [6]. In contrast, one three year prospective study of intrathecal opioid treatment for CNMP found that in patients with extremely severe pain, although likely to improve, their overall severity of pain and symptoms still remained high [7].

There are two randomised double blind placebo controlled trials supporting the use of ziconotide in the treatment of CNMP; however clinical significance was modest, side effects were problematic and experience is limited. Further high quality studies and longer term data experience is still limited [8] [9].

2.2 Cancer pain

There is a systematic review which supports intrathecal opioid therapy for pain that has not been adequately controlled by systemic treatment [10].

There has been one comparator study describing superior efficacy of intrathecal drug delivery compared with conventional medical management [11]. There are numerous case reports describing the efficacy of neuraxial drug delivery in cancer patients.

Smith et al [11] [12] [13] 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. Although longevity was not an outcome measure, Smith et al 2005 [12] demonstrated that at 6 months 53% of the ITDD arm were still alive compared to 32% of the conventional medical management group. This result is from an ‘intention to treat analysis’.

There are several reasons why longevity might be increased including improved mobility and alertness. There is also laboratory evidence that systemic morphine inhibits the immune system [14]. Morphine given systematically might therefore adversely affect survival in a cancer population when compared with intrathecal analgesia.

There is a randomised controlled trial which demonstrates the usefulness of intrathecal ziconotide in the treament of refractory pain in patients with cancer or AIDS [15]. Again, clinical experience is limited, side effects are problematic and longer term data is awaited.

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 [16] [17] [18] [19] [20] [21].

2.4 Cost effectiveness

There have been a variety of economic studies of intrathecal pumps ranging from cost modelling [22] to cost utility analyses [23]. It appears that this therapy is more cost effective than systemic medication beyond 3-6 months for cancer pain and beyond 11-22 months for non-cancer pain. For spasticity, in carefully selected patients who have not responded to less invasive treatments, continuous intrathecal baclofen is likely to lead to worthwhile functional benefits and has an acceptable cost / benefit ratio compared with other interventions [24].

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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), 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, on going management, and assessment of response. Early attention should be given to the familiarisation of theatre 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 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 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] [2] [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 pump. Stability and compatibility of admixtures must be addressed (see section 8.7).

3.5 Some preparations which are currently used do not have product licences for ITDD. Guidance must be followed for the use of unlicensed drugs. 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 Extreme vigilance must be given to all aspects of safety, particularly the prevention of the inadvertent administration of drugs by the wrong route. Design of systems and equipment 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 should be available (appendix 1).

3.10 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 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. A national database and network of regional centres would 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, particularly mechanical back pain that has not responded to stabilisation procedures, mixed cases of nociceptive and neuropathic pain, and cases of widespread pain eg back and bilateral leg pain. A recent retrospective study by Raphael et al 2002 [1] concluded ITDD systems appeared to confer benefit over spinal cord stimulation in the failed post surgical spinal pain and chronic mechanical back pain patient but recommended a prospective study.

4.1.2 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 implantation; and ii) to consider what additional individualised preparation might be advisable for the patient [2].

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 behaviour.

4.1.4 In the opinion of the working party, for this group of patients, a trial of intrathecal therapy should always be performed. This can be by means of bolus or infusion but the former give limited information. There is no ideal screening method [3]. There are established methods of extrapolation of effective trial doses to 24 hour dose to be infused.

4.2 Cancer Pain

4.2.1 Cancer pain can be controlled in the majority of patients by following the WHO guidelines [4] [5] [6]. However, 10-20% will require more intensive measures to control pain. In a prospective study of 2118 patients with cancer pain managed by the WHO guidelines, 8% required nerve blocks, 3% neurolytic blocks and 3% spinal analgesia (epidural/intrathecal) [5]. 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 cancer patients is failure of conventional routes of administration of analgesics to achieve satisfactory analgesia despite escalating doses of strong opioids, and/or dose limiting side effects [7]. 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 Historically, the epidural route has been the more commonly used route for continuous neuraxial drug delivery in cancer pain. However, there are reports of improved pain control and fewer complications with the intrathecal route [8] [9] [10]. 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 [9]. Similar infection rates have been reported with intrathecal or epidural administration [11] but there is evidence that intrathecal catheters are safer when they need to be in place for more than three weeks [12] [13].

4.2.5 Neurolytic or neuroablative interventions may be appropriate alternative interventions.

4.2.6 ITDD currently appears to be underused in cancer pain 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 Pumps 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.

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 has 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.

5.4.4 The system is battery driven and battery life varies typically from 5-8 years.

5.4.5 Regular attendance for refilling is required.

5.5 Patients with spasticity can be managed with a fixed rate delivery system when frequent alteration of dosage is not required.

However where dose variations between day and night are required or where variations in dose to cope with rapidly progressive disease as in MS, are needed, a programmable system is desirable. As one of the key features of intrathecal baclofen therapy is the fine line between too little and too much, a programmable pump may be required.

5.6 External pumps 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.

In the opinion of the authors fully implantable systems are underused in cancer patients.

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6 Procedure

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 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].

6.1.3 When drugs are to be used intrathecally, their systemic use will need to be discontinued preoperatively. Management of potential withdrawal effects should be planned.

6.1.4 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.

6.1.5 There is little published evidence regarding the use of antibiotic prophylaxis. The consequences of infection justify detailed audit of current practice and outcomes, and research to provide evidence based guidelines at a later date.

6.1.6 Refill intervals have to be planned with regard to the stability of the chosen drug in solution.

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

6.1.8 Baseline endocrine function should be measured by testosterone and luteneizing hormone (LH) levels in men and oestradiol, progesterone, LH and Follicle Stimulating Hormone (FSH) levels in women. These tests should be repeated annually.

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 [2]. Details of operative technique can be found elsewhere [3]

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7 Aftercare

7.1 Inpatient management

7.1.1 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.

7.1.2 The patient should not be cared for on a ward where there are MRSA infected patients.

7.1.3 Mobilisation should start as soon as appropriate.

7.2 Discharge and ongoing care

7.2.1 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.

7.3 Some ITDD systems are at risk of significant damage and malfunction from MRI scanners. Under some circumstances patients with fully implanted intrathecal drug delivery systems can have MRI scans. 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. Programmable systems should be stopped prior to the scan and then recommenced once the MRI scan is completed. Patients with fixed rate delivery systems pose more of a problem; these 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 opioid withdrawal and an increase in pain and spasm will have to be addressed.

7.4 Scanners in airports and shops should be avoided; patients are able to show a card to accommodate this.

7.5 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.

7.6 Advice should be taken from the implanting clinician before deep sea diving.

7.7 Short wave diathermy should be not be used within 30 cm of the pump or catheter.

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

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 Morphine is considered the 'gold standard' because of it 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.

In a recent study, it has been found that di-acetyl morphine immediately starts to decay to mono-acetyl morphine in implanted Synchromed pumps with half- life of 50 days. 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.

There have been two case reports of precipitation of diamorphine in the Synchromed pump when used in high concentrations, leading to malfunction of the pump. A consensus of many pain consultants in the UK has recommended that it is inadvisable to use diamorphine in a new implanted programmable Synchromed pump. The patients with diamorphine in their Synchromed pump should be changed to an alternative medication. (Pain Society Newsletter Summer 2004). Diamorphine can be used in constant flow pumps where its high solubility is valuable.

8.1.4 Centrally mediated side effects of intrathecal opioids include late respiratory depression [4], pruritis, nausea, vomiting, urinary retention, sedation, constipation, oedema, weight gain, excessive perspiration, memory or mood changes and headache.

8.1.5 Endocrine effects include hypogonadotrophic hypogonadism, loss of libido and hypocortisism [5].

8.1.6 Intrathecal catheter tip inflammatory masses have been described. There are more than 500 known cases worldwide. The incidence is estimated at 0.5% for a patient. They are found between the spinal cord and the dura and occur mostly in the thoracic area. They 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 aetiology is unknown, but may be a reaction to the catheter tip, or a low grade infection or possibly may be a reaction to infused medication. Animal models suggested highly concentrated opioid as the cause. It is not clear if total daily dose or concentration of morphine is important. However infusion of saline did not result in masses. There is a possible protective effect from clonidine added to morphine in animal models, but this has not been confirmed clinically in man. Masses have been reported with morphine, hydromorphone and baclofen. Low pump flow rates may be a risk factor. There should be a low index of clinical suspicion if failure of analgesia, radicular pain, altered bowel or bladder function or neurological signs occur. There should be early involvement of neuroradiological and neurosurgical expertise. Turning off the infusion for a period of weeks to months may be enough to allow a catheter tip mass to resolve. Revision or removal of catheter may be necessary. If cord compression has occurred, spinal decompression and removal of granuloma may be necessary [6] [7].

8.2 Intrathecal local anaesthetics

8.2.1 Intrathecal bupivacaine is used in the treatment of CNMP and cancer pain [8] [9] [10] [11]. 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 [12] [13] [14].

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 bupivaciane 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 [17] [18]. 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 [19] [20] [21].

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 [22]. 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 [23] [24].

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 maybe 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 [25].

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 can 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 [26]. However, an expert panel recommends a lower dosage at 0.5 mcg/day increase by 0.5mcg steps every week [27].

8.5.3 Mixtures of ziconotide with other intrathecal medications including morphine, hydromorphine, clonidine and baclofen are associated with reduction in ziconotide concentration of the order of 20% within a few weeks [28] [29] [30].

8.6 There is no high quality evidence to support the use of aspirin, NMDA antagonists, neostigmine, somatostatin, octreotide, midazolam, droperidol, Non Steroidal Antiinflammatory 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 [31] [32] [33] [34] [35].

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9 Complications

9.1 When selecting patients potential complications should be considered and addressed in informed consent. Serious procedure and device related complications are rare. Minor complications are common. In a population of cancer patients, catheter, procedure, device-related and illness-associated adverse incidents occurred at a rate of 0.45 events per patient year [1].

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.

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. There are also reports of permanent neurological damage following intrathecal local anaesthetic administration [2].

9.4 Possible infections include meningitis [3] epidural abscess pump pocket infection or pump reservoir infection [4].

9.5 Cerebrospinal fluid leaks, hygromas and post dural puncture headaches have all been reported [5]. 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 overfill or incorrect refill.

9.7 Troublesome problems can occur with the pump pocket or the scar eg 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 [6].

9.9 In cancer pain analgesic failure rates are high, about 30% [7] and complication rates about 45% [8]. A high proportion of patients who report failure or poor outcome with this technique will have epidural metastases or spinal stenosis. [6].

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Polyanalgesic Consensus Conference 2007

2007 POLYANALGESIC ALGORITHM FOR INTRATHECAL THERAPIES

Line #1:	**(a)** morphine	↔	**(b)** hydromorphone	↔	**(c)** ziconotide
Line #2:	**(d)** fentanyl	↔	**(e)** morphine / hydromorphone + ziconotide	↔	**(f)** morphine / hydromorphone + bupivacaine /clonidine
Line #3:	**(g)** clonidine	↔	**(h)** morphine / hydromorphone / fentanyl bupivacaine +/ clonidine +ziconotide		
Line #4:	**(i)** sufentanil	↔	**(j)** sufentanil bupivacaine +/ clonidine +ziconotide		
Line #5:	**(k)** ropivacaine, buprenophine, midazolam meperidine, ketoralac				
Line #6:	***Experimental Drugs*** gabapentin, octreotide conopeptide, Neostigmine, Adensoine XEN2174, AM336, XEN, ZGX 160				

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