NHS England

Clinical Commissioning Policy: Intrathecal Pumps for treatment of severe chronic pain

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Contents

Policy Statement

NHS England will commission in accordance with the criteria outlined in this document.

In creating this policy NHS England has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

This policy document outlines the arrangements for funding of this treatment for the population in England.

Equality Statement

Throughout the production of this document, due regard has been given to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited in under the Equality Act 2010) and those who do not share it.

Plain Language Summary

Intrathecal Drug Delivery plays an important role in the treatment of intractable pain in highly selected patients.

Intrathecal Drug Delivery (ITDD) enables clinicians to formulate individualized treatment regimens that can provide effective analgesia (pain relief) with smaller doses, and with potentially fewer adverse effects than traditional opioid-based (morphine & morphine - like) therapies in highly selected patients.

NHS England will routinely commission the use of ITDD to treat highly selected patients with severe refractory pain of non-cancer origin. There is a high unmet clinical need for this service that is supported by evidence on clinical efficacy and safety. Use of this therapy will be commissioned by NHS England as a prescribed service in highly specialised pain centres acting as lead centres for agreed geographical pain networks, to ensure both the right patient selection, follow up and strict clinical vigilance and safety arrangements.

ITDD is used equally in patients with limited life expectancy as those patients with near normal expectancy. All will have had severe refractory pain. It is a combination of the selection processes, ITDD Team expertise, associated support network and overall centre organisation and specialised pain centre status, that makes therapy with ITDD successful. This is a last resort treatment for patients with severe unremitting pain. There is evidence to show that ITDD treatment is associated with significant and sustained improvements in pain, function, disability, employment and quality of life. The research also shows significant cost- savings longer term

compared with conventional pain therapy. Whilst the research is mainly observational, it comprises several studies and is endorsed by the specialized interventional pain consultants who provide this service.

1. Introduction

Intrathecal drug delivery (ITDD) offers a late resort alternative for a small cohort of patients with chronic non-cancer pain with a specific pain problem, who fail to obtain pain relief from systemic drug administration, interventional procedures and psychological and physical interventions. Examples include patients with osteoporosis with multiple vertebral collapse or spinal stenosis not amenable to surgery, some cases of neuropathic pain such as post amputation pain refractory to neurostimulation. A small number of patients receive intrathecal drug delivery due to severe and sustained toxicity to systemic opioids. The intrathecal route also enables pain clinicians to use much smaller opioids doses and combine opioids with drugs that cannot be administered systemically such as local anaesthetics and clonidine. This reduces cost and side effects associated with larger doses of individual drugs.

Long-term administration of systemic opioids at high doses has been associated with tolerance, opioid induced hyperalgesia, suicide risk, depression and sex hormonal suppression. While long-term administration of ultra-low dose intrathecal opioid for non-cancer pain has been shown to be effective, the effectiveness of oral long-term opioids has been questioned in a number of recent population surveys.

ITDD systems are an advanced stage intervention and are only indicated where other conservative pharmacologic, physical and psychological interventions have failed or are contraindicated and where the uncontrolled pain is causing a significant impact on physical and mental health. By positioning a catheter in the cerebrospinal fluid, ITDD allows smaller doses of drugs to be applied directly to the receptors of the central nervous system, achieving pain relief with much smaller doses and as a consequence fewer side effects, than with oral or parenteral routes. Intrathecal opioid delivery by an implantable pump improves pain relief, increases function and enhances patient quality of life. ITDDs achieve higher drug concentrations with the delivery of smaller drug doses into the CSF, sparing the undesired secondary effects of these same medications when administered by other routes.

History: Opioid receptors were identified in the spinal cord in 1973[i]. Subsequent animal studies demonstrated that intrathecal opioids produce powerful and highly selective analgesia[ii]. Cousins in 1979 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[iii]. The first clinical use of epidural and intrathecal opioids followed[iv,v]. 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 transported via the cerebrospinal fluid[vi].

Intrathecal Drugs: Intrathecal baclofen (and ziconotide currently subject to an NHS England CtE application) are approved for this use by EMEA. Other drugs such as morphine, bupivacaine and clonidine although routinely used in clinical practice have never been licensed for the purpose. Drug types and combinations are agreed by international panel of experts and are published in polyanalgesic consensus

conference 2012 as well as the British Pain Society Guidelines on intrathecal drug delivery (Table 2).

Intrathecal opioids e.g. 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.[vii]

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.

Intrathecal clonidine, an α2 agonist, modulates pain transmission by suppression of the release of the C fibre neurotransmitters, Substance P and Calcitonin Gene Related Peptide (CGRP). It has been hypothesised that clonidine also suppresses preganglionic sympathetic outflow.

Ziconotide is a neurone specific calcium channel antagonist acting on calcium receptors f at presynaptic terminals in the dorsal horn of the spinal cord[viii]. Intrathecal ziconotide is thought to produce its analgesic effects by blocking neurotransmitter release in primary nociceptive afferent fibres. Ziconotide can only be given as a continuous intrathecal infusion using ITDD. Ziconotide is not routinely funded by NHS England, however the CRG is considering an application to the Commissioning Through Evaluation (CtE) scheme in order to gather more evidence in certain patient groups such as young patients with a long life expectancy and those who are intolerant to opioids.

Polyanalgesic algorithms for the stepped use of intrathecal therapies have been published.

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

- specialist MDTs and institutions delivering or planning to deliver the treatment
- referrers, secondary care, primary care, health professionals and carers regarding the management of patients with implanted intrathecal drug delivery (ITDD) systems
- Commissioners of health care as to the nature of the technique and when it might be used

The document describes the policy for the commissioning of ITDD systems for clinical use in the management of non cancer pain and provides recommendations for the clinical and governance context in which this therapy should be delivered.

It covers the clinical indications in which pain relief is the major indication for the technique.

These recommendations are based upon synthesis and interpretation of published evidence and upon the consensus of expert opinion of the Clinical Reference Group for Specialised Pain.

2. Definitions

- Intrathecal drug delivery system/PUMP for Drug delivery (ITDD) – In this policy ITDD is the name of the treatment and device.

  -Intrathecal catheter – Part of an ITDD device that is placed within the spinal cerebrospinal fluid (Subarachnoid space) to infuse pain medication stored in the pump reservoir. It is inserted via a needle, as a percutaneous technique or via a cut down open procedure.

  -Implantable pump reservoir – Contains the drug, which is infused in to the cerebrospinal fluid and a power source that drives the pump. Programmable pumps allow variable flow to more easily titrate dose and match infusion rates based on pain variation are the gold standard of ITDD.

- Trial of ITDD – A test period by which the patient can experience pain relief and improvement in function from a temporary application of drug to the cerebrospinal fluid. The result from the trial is useful towards the decision making process for permanent implantation.

- Severe, Chronic Pain - Chronic pain which is continuous, long-term pain of either more than 12 weeks (6 months, 12 months according to other definitions or after the time that healing would have been thought to have occurred in pain after trauma or surgery.

- Intractable pain – Pain, which despite expert management is unresponsive or poorly responsive to conventional medical management or where the conventional pain relief causes unacceptable side effects.

- Neuropathic pain is pain initiated or caused by a primary lesion or dysfunction in the peripheral or central nervous system. For example pain following shingles, brachial plexus avulsion, amputation, or spinal cord trauma. Pain that occurs in diabetics or in patients with multiple sclerosis can also be neuropathic.

- Nociceptive pain - Pain caused by damage to tissues.

- CNMP: Chronic non-malignant pain or non-cancer pain.

Examples of chronic non cancer pain indications

- Severe pain associated with multiple osteoporotic fractures of the spine not amenable to interventions and unresponsive to titration of systemic opioids.
- Neuropathic pain resulting from partial spinal cord injury/disease, brachial plexus avulsion and post amputation phantom pain. While some of the above are susceptible to neurostimulation, a subset of severe neuropathic pain are refractory to neurostimulation and responsive to ITDD.
- Complex regional pain syndrome with a poor response to neurostimulation and a dominant element of dystonia.

- Chronic severe postsurgical and posttraumatic pains refractory to spinal cord stimulation trial, appropriate opioid titration, interdisciplinary rehabilitation and non-pharmacological methods of pain relief.
- Failed back surgery syndrome was historically the largest cohort of patients managed on long term ITDD. With advances in neurostimulation technology and its application fewer of these patients require ITDD.

- Outcome measures – Measures of pain and pain relief, change of function, improvement in quality of life, reduction in oral pain medications and decrease in toxic side effects from systemic drugs.

- Outcome Indices will include BPI (Brief Pain Inventory), Visual Analogue Scale for Pain, NRS (Numerical Rating Scale), SF-36, BDI (Beck Depression Inventory), PDI (Pain Disability Index), BPI (Brief Pain Inventory), EQ5D-5L, MPQ (McGill Pain Questionnaire), Patient's Global impression of change, patient assessment within three months of referral.

- The National Neuromodulation Registry (NNR) will be available for the systematic collection of patient and device data on demography, disease severity and outcomes for all patients implanted with ITDD. The outcomes used are BPI, EQ5D-5L, Global impression of change, Intrathecal drug combinations and daily doses.

- NNR is sponsored by the Neuromodulation Society of UK and Ireland (NSUKI) and has been created in partnership with the National Institute of Cardiovascular outcomes and Research (NICOR)

- Timing of assessment - (IASP recommendations[ix] as below)
  a. Acute painful conditions should be treated immediately (e.g., painful sickle cell crises and pain related to trauma or surgery)
  b. Most urgent (1 week): A painful severe condition with the risk of chronicity or deterioration, such as the acute phase of complex regional pain syndrome (CRPS), pain in children, or pain related to cancer or terminal or end-stage illness.
  c. Urgent or semi-urgent (1 month): Severe undiagnosed or progressive pain with the risk of increasing functional impairment, generally of 6 months' duration or less (back pain that is not resolving or persistent postsurgical or post-traumatic pain).

Routine or regular (8 weeks): Persistent long-term pain without significant progression.

3. Aim and objectives

This policy aims to :

- Present the policy recommendations and rationale.

The objectives are to:

- Assess the evidence base on the efficacy and safety of Intrathecal Pumps (ITDD) in the treatment of severe, chronic non-malignant pain (CNMP).
- Achieve a clinical consensus
- Derive policy recommendations for implementation

4. Epidemiology and needs assessment

The Health Survey for England (2011)[11] published in December 2012 highlights that current service provision for pain management is inadequate and existing services are not evenly distributed across the country. The Chief Medical Officer's Annual Report (2008) also had similar view on pain services provision in England. In order to look at the quality and provision of existing pain services, the National Pain Audit was commissioned. The report from phase one of the audits has highlighted that there are areas to be improved, particularly around the provision of multidisciplinary services for pain management.

Historical studies of the time trends in pain prevalence have highlighted the increase in prevalence of pain[12]. Harkness et al studied two cross sectional population surveys in the North of England undertaken 40 years apart which showed a significant rise in musculoskeletal pain. Similarly US researchers have found an increase in severe chronic impairing back pain in North Carolina from 4% to 10% in surveys conducted between 1992 and 2006 (Freburger et al 2009)[13]. For many patients, pain produces severe distress dominating and disrupting their quality of life. If the focus is narrowed to disabling chronic pain then estimates vary from 6 to 12% (Croft et al. 2010)[12].

More women than men reported chronic pain. Overall, 31% of men and 37% of women reported this. The prevalence of chronic pain increased with age, with older people being more likely to report chronic pain than younger people. In those aged 16-34, 14% of men and 18% of women reported chronic pain. This rose to 53% of men and 59% of women aged 75 and over[x]. The Royal College of General Practitioners made chronic pain a clinical priority area for 2011-2014, appointing a clinical champion to oversee the work.

European data as in table 4, reflects poor uptake of ITDD treatment generally in UK. This has to be considered in the context of the intractable nature of symptoms, disability and cost-effectiveness data now available for spasticity and chronic pain.

HES data and expert opinion suggests that 100 new patient ITDD pumps for Pain (about 50 for non-cancer pain) are implanted annually. Expert opinion suggests that there are currently 1000 patients who are using ITDD for non-cancer pain. These patients need to be maintained in addition to the new patients.

5. Evidence base

A literature review of the evidence and a summary is presented below.

A literature search restricted to randomised control trials and systematic reviews was undertaken and a summary of the evidence is presented below.

Non- cancer pain

Clinical effectiveness and safety

The evaluation of the data for intrathecal drug delivery has to be viewed with an awareness of a number of factors that limit the ability of researchers to conduct large scale clinical trials in this field:

The small numbers of ITDD procedures for non-cancer pain carried out in the UK 50-100/annum due to its position as a late resort intervention.

There are barriers to conducting investigator led STIMPS (Clinical trials of investigational Medicinal Product), which are compounded by the need to use "special order" higher concentrations of preservative free preparations of drugs suitable for the intrathecal route and compatible with the pump.

The lack of licensing for a number of drugs including opioids despite routine use in clinical practice.

Two systematic reviews and one RCT were identified.

One systematic review was identified which evaluated the efficacy and safety of intrathecal infusions used in long-term management (> 6 months) of chronic refractory cancer pain and non- cancer pain Hayek et al. 2011)[14]. The search period covered 1966-2010. It identified 5 studies in total for cancer, which met its inclusion criteria - 1 randomised controlled trial (RCT) and 4 observational studies. For non-cancer pain, 15 observational studies were identified that met the inclusion criteria (8 prospective studies and 7 retrospective studies) for a minimum of follow up of 12 months. The authors concluded that the recommendation for intrathecal infusion systems for cancer-related pain is moderate recommendation based on the high quality of evidence. For non-cancer pain the recommendation was limited to moderate.

The second systematic review evaluated the evidence (from 1966-2012) for intrathecal infusion systems for short (12 months) and long-term management (>12 months) of chronic non-cancer pain[15]. A total of 7 non-randomised studies met inclusion criteria. Overall, the 7 studies evaluating intrathecal infusion systems reported pain relief and improvement in function. There were 6 studies that showed positive results for long-term pain relief at ≥ 12 months. There were 3 studies that showed positive results for short-term relief at ≤ 12 months. Significant improvement in function was also reported in 5 of the 7 studies both short-term ≤ 12 months) and long-term at ≥ 12 months. In the 7 studies, vast majority of complications reported were minor, however some serious complications did occur. An increased mortality rate in patients with non-cancer pain receiving intrathecal opioid therapy (mortality rate of 0.088% at 3 days after implantation, 0.39% at one month, and 3.89% at one year) was identified as likely related to the opioids as well as other factors that may be mitigated especially at the start of therapy. Other serious complications include granuloma formation that may be related to the amount and concentration of

opiates, mostly morphine and hydromorphone. Other complications of ITDDS include catheter kinking, catheter fracture/leakage, catheter migration, cerebrospinal fluid (CSF) leak, seroma, hygroma, infection, pump erosion through the skin, and medication side effects. Based on the appraisal of the evidence, the authors concluded the evidence for intrathecal opioid infusion therapy is limited (based on observational studies) for short-term and long-term pain relief and functional improvement in the treatment of chronic non-malignant pain.

In the RCT (Raphael et al 2013) aimed to investigate the efficacy of intrathecal morphine 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[16]. 15 patients were randomised to control (n=5) or intervention (20% dose reduction (n=10) and included in an intention-to-treat analysis. Owing to worsening of pain, seven patients (in the intervention arm) withdrew from the study prematurely, none withdrew from the control arm. The 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-=8) conducted at a single centre.[16]

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 ITB. 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.[17]

Duarte et al followed up a cohort of 20 patients with chronic non-cancer pain treated with IDDS for an average 13 years. 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.[18]

Cost-effectiveness

Patients with pain of non-malignant origin often require treatment for several years. ITTD is often reserved as a late-resort therapy. Cost categories include pre-implant costs, implant procedure costs (OT, hospital stay, Equipment), post implant (maintenance, dose adjustment, drug refill, conventional pain medications) and complications. A Canadian study averaged the above costs annually over a 5 year period in two randomised groups - CPT and ITDD. Patients had failed back syndrome with a mean of 3.3 operations and one year continuous work absence. Both groups had 44 patients each. The number of patients who received a

permanent ITDD implant following a successful trial response of ≥ 50% pain-relief was 23/44. The mean hospital stay for implantation was 6.24 days and the mean number of complications per implant was 0.77. Cumulative costs per year for a 5 year period totalled $29,410. This included pump replacement for battery depletion. There was no further surgery of the lumbar spine in this group. In the CPT group 5 year costs totalled $38,000 due to higher costs for pharmacotherapy, adjunctive therapies, break- through pain needing hospitalization and referrals to other allied health professionals [19].

ITDD was shown to be cost-effective both in the best and worst-case scenarios. In the best case scenario, the break-even point occurs at 26 months and in the worst-case scenario at 30 months. The mean 5 year VAS pain relief score was 61 ± 5.2% with an improvement in disability of 27%. (compared with 12% in the CPT group). Factors increasing cost-effectiveness were identified as patient selection, cost of pump, battery life and complications. The majority of the cost of ITDD is incurred at inception of the therapy. However the low costs of maintenance dramatically decrease the overall costs over long-term therapy [19].

Another US study showed the system cost of implanting and maintaining a pump to be $10 per day. The same study observed the median longevity of a pump to be 5.9 years. This was shortened with earlier replacement due to surgical or infectious complications. The latter will be reduced by proper patient selection and proper surgical technique[20]. A simulated cohort of 1000 patients treated for 60 months showed that the cumulative cost of intrathecal morphine delivered with an ITDD Pump is less than the cost of medical management after 22 months and 11 months for base care (usual Medicare Fee) and best care scenarios, with a total 5 year cost of $82,893 and $53,468 respectively against $85,186 for medical management.[21]

6. Rationale behind the policy statement

It is acknowledged that severe, chronic refractory pain represents a therapeutic challenge and an area of high unmet need for which additional treatment options would be welcomed. For both chronic non-cancer pain and cancer pain, the individual studies included in the two Systematic Reviews, showed substantial and significant improvements in pain relief, mood scores, QOL, function, physical activity and reduction in disability and oral opiate intake.

It has to be recognised that conduct of RCTs in the field of intrathecal drug delivery is a significant challenge due to small numbers of candidates, labour intensive nature of the therapy and challenges of conducting research in an area of treatment requiring "special" preservative free high concentration preparations of drugs.

Thus the numbers of RCTs for non-cancer pain is limited: a small study that demonstrated that withdrawal of intrathecal opioids resulted in an increase in VASPI scores in the majority of patients causing them to withdraw from the study.

A more recent trend in ITDD of ultra low dose infusions to avoid tolerance and opioid induced hyperalgesia has shown sustained benefits in prospective case series of 61 patients followed up to 3 years. Over the latter follow up period, there was only a small increase in dose of intrathecal opioids and a large reduction in the

use of oral opioids.

Finally for or non- cancer pain, systematic reviews have concluded that the recommendation is limited to moderate' based on observational studies and lack of RCTs.

The expert consensus opinion of the CRG is that it would be unethical to exclude non -cancer patients from funding for ITDDs on the basis that while the aetiology of the pain may be different, the mechanisms of pain and experience of pain are similar to cancer related pain. In an age of increasing cancer survivors there are increasing numbers of patients with difficult to treat mixed neuropathic and nociceptive pain as a result of their cancer treatment with near normal life expectancies. The distinction between cancer and non-cancer related pain is blurred.

7. Criteria for commissioning

Overview

ITDD for non-cancer related pain will be reserved for a small number of highly selected patients that meet the same stringent criteria and have been assessed at a highly specialised pain management service or a designated experienced centre linked to a highly specialised pain management service as part of an Operational Delivery Network (ODN). In addition to careful clinical selection, a trial of intrathecal drugs will be performed. The nature of the trial will be appropriate to the needs of the patient. This will be accompanied by a rigorous and objective assessment of pain relief and improvement in function.

It is anticipated that the use of ITDD for non-cancer pain will be for a smaller number of patients than for cancer pain. Hospital Episode statistics data show that 50 patients were implanted with ITDD for non-cancer pain in 13/14. Patients with severe refractory non-cancer pain may have near normal life expectancies. This is in contrast to cancer related pain patients. However with increasing success of cancer therapies, more patients are living longer with their cancer in remission but with the consequence of chronic pain.

Proper patient selection, implantation technique, maintenance and continued clinical and equipment vigilance are paramount to ensure success and reduce complications.[22]

Moreover all future ITDD treated patients will be entered onto the National Neuromodulation Registry to allow a long term observational audit of outcomes.

The use of ITDD to treat severe chronic pain will be routinely funded for intractable non - cancer related pain for the following selected group of patients with intractable pain:

Indications and contraindications

Patients who meet all of the following criteria:

- Patients who have severe pain of known origin that has failed to be satisfactorily managed despite conventional and specialised pain management or where that pain control is partially achieved but with unacceptable toxic side effects.

- All patients will have been previously assessed by a multidisciplinary pain management service with expertise in intrathecal therapy, and following an adequate trial of oral/transdermal opioids which achieve some pain reduction but their continued use is limited by high opioid toxicity.

- Clear aetiology of chronic, non-malignant pain (such as brachial plexus avulsion, end stage osteoporotic fractures, spinally mediated neurogenic pain, visceral hyperalgesic syndromes, dystonic CRPS) unresponsive to other medical and advanced interventional/surgical pain management treatments, will be candidates for ITDD. Many of these patients will have mixed pain aetiology (neuropathic and nociceptive pain). Some may have failed with a trial of spinal cord stimulation (SCS) or SCS is unfeasible.

- Patient has been referred to and has been assessed and is under the care of a Tertiary Highly Specialised pain management centre and MDT (with expertise, experience, follow up capability, and staffing levels to support the safe use and delivery of ITDD, on a 24/7 basis).

- Patient has received a structured pain assessment with an accurate formulation of both psychological and physical factors contributing to pain by the multi-disciplinary team experienced in ITDD therapy[xi]. This will include baseline pain characteristics, pain intensity and severity scores, prior medications (anticoagulants, chemotherapy etc), alcohol/recreational drug use/abuse, co-existing medical conditions, infection risk, immunosuppression, concurrent pain medications and psychological evaluation for stability. Other patient selection criteria will include consideration of social and medical support systems, prognosis and life expectancy.

- Patient has undergone a successful trial of the intraspinal opioids with an emphasis on side-effects and efficacy.

Exclusions

Patients who meet with any of the following criteria should not receive ITDD.

- Absolute contra-indications are:

- Pregnancy or nursing mother or planning to get pregnant

- Any concomitant treatment or medical condition that would render ITDD administration hazardous
- Lack of social support or difficulties with attending refill appointments
- Uncorrectable bleeding disorder
- Logistical difficulties with after care including pump refills, funding of ongoing ITDD.

8. Patient pathway

The following pathway criteria will have to be fulfilled:

Referrals

Referrals to MDT lead of highly specialised pain centre only from networked secondary care pain services or other tertiary specialties e.g. pain centre, orthopaedic (trauma, spinal). This should be a tertiary referral service.

MDT

There should be a designated team that comprises the pain specialist, the implanter, typically an interventional pain specialist or neurosurgeon, nurse specialist, aseptic pharmacy facilities, psychologist and physiotherapist as appropriate with specialised training and experience in the field. All those involved in implantation, follow-up and refill procedures must maintain appropriate continuous professional development.

It is recognised that the management of each condition is highly specialised. The specialised team will work jointly with the patient's primary care team, referring secondary care pain teams and with the clinical teams with responsibility for the primary condition. All MDT professionals have a role in patient assessment, choice of therapy, assessment of response and continuous management. The MDT should assess the potential benefits and risks of ITDD for the individual patient and discuss them with the patient. The patient and carers must be a part of decision making.

Treatment, Monitoring and Follow-up

All reversible and treatable causes of pain should be addressed before ITDD is undertaken. This should include the appropriate application for a sufficient duration of less invasive pain management therapies before initiation of ITDD. The patient's narrative should be supplemented by objective records from referring clinicians.

A thorough physical examination including spinal examination and for co-morbidities that could increase the risk of ITDD should be carried out. Co-morbidities such as Obstructive Sleep Apnoea, diabetes, obesity, metabolic syndrome or chronic lung, cardiac or kidney disease or smoking will increase the risk of complications. All comorbidities should be well managed before commencing ITDD therapy.

Patients with a severe, chronic pain diagnosis may also have depression, anxiety,

PTSD, substance abuse concerns, cognitive impairment or personality disorder. Hence anyone being considered for ITDD should have a psychological examination as an essential aspect of patient selection. CBT and psychological support should be available.

Final approval of a patient's suitability for ITDD rests with the MDT.

Comprehensive patient/caregiver education (on efficacy, side-effects of ITDD, risks and benefits) and informed consent are essential elements of the process. Patients should also know that achieving an appropriate balance between pain management (optimisation) and side-effects (minimisation) takes time and may require slow titration with continuing adjustments. Patients should understand that the outcome of ITDD is one of pain management and not of pain cure. Patients must be made aware of the use of drugs outside license where this is the case and its implications as per the British Pain Society guidelines. ITDD requires a candid therapeutic partnership in which the patient takes responsibility for adherence to the physician's recommendations, self-monitoring and vigilance for adverse effects. A patient who cannot partner in this way or who does not have a caregiver who can fulfil this role should not be implanted.

Endocrine evaluation, as guided by an endocrinologist should be undertaken before starting intrathecal opioid therapy as treatment affects the hypothalamic-pituitary adrenal/gonadal axes.

Persistent lower limb oedema is a poorly understood side effect of intrathecal opioid administration but may relate to ADH homeostasis. This is usually managed by opioid rotation or substitution where persistent.

All patients considered for ITDD should have a trial. A trial provides an opportunity to assess short-term pain relief, gauge dosing, determine individual tolerability, and assess an individual's response to ITDD and also to monitor patient safety.

Patients with intrathecal implants require ongoing attention and care including programming, prescription adjustments, refills, monitoring of efficacy and disease progression. Dose increases should be titrated slowly to minimize adverse effects and allow patients to develop tolerance. Dose increases should not generally occur more frequently than once weekly intervals and should not exceed 30% of the total infused daily dose. More rapid dose titration may be suitable for patients with cancer pain. At every refill, patients and care-givers should be reminded about the symptoms and signs of overdose, underdose and withdrawal and instructed to seek medical assistance should they experience these. Patients should be observed for at least 30 minutes after pump refill.

These resources must be planned and arranged appropriately. Dedicated refill sessions are recommended, conducted by suitably trained and competent nurse specialists or doctors, in dedicated sterile facilities with full in-patient monitoring support and imaging support. All programmed prescriptions should be double checked by a competent nurse or doctor before the patient leaves. As complications are potentially life threatening, arrangements must be in place for 24/7 medical cover. Those undertaking refill procedures should be familiar with the

technique and aware of the importance and significance of neurological symptoms and signs, failure of pain relief and also the clinical signs of overdose.

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. Patient and carer engagement in checking the route should be encouraged. Drugs and drug mixtures for intrathecal use should be pre-prepared in appropriate sterile conditions, be preservative free and be compatible with the pump. Stability and compatibility of admixtures must be addressed. Off label use of drug admixtures (only as recommended in Polyanalgesic consensus - PACC) should be carefully explained to the patient. The reasons for such use and the possible sequelae explained and documented. In many situations, better efficacy and reduced side effects are achieved with appropriate drug admixtures.

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.

Education of the primary care team, patient 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.

Complications and Their Management

At each visit patients should be encouraged to report and should be examined for any changes in pain perception and new or worsening side-effects.

Patient education should cover the clinical signs of overdose, including dizziness, sedation, euphoria, anxiety, seizures and respiratory arrest.

ITDD – associated respiratory depression can be serious. Hence it is important for the supervising clinician to be aware of and manage all of a patient's CNS – active medications. Non-essential CNS medications may need to be eliminated. Communication with other treating physicians may be needed.

When starting intrathecal therapy, eliminate systemic opioids if possible or reduce them by at least 50% when elimination is not feasible. Start with low doses and escalate slowly. The goal of fine-tuning the opioid dose is to reach the lowest effective dose to minimise side-effects. The most common side-effects of intrathecal opioid therapy - pruritis, nausea and vomiting, urinary retention and constipation frequently appear at the start of therapy, usually can be managed and generally resolved during the first three months of IDD therapy.

Respiratory depression can be detected and treated if a patient is monitored following the start or restart of opioid therapy. Treatment cessation followed by refill or delayed refill and resumption of previous dosing can cause respiratory depression, due to loss of opioid tolerance. Respiratory depression is an opioid dose-dependent phenomenon whose risk is also increased by co-morbidities such

as obesity, illicit drug abuse and the use of other CNS depressants. Intrathecal therapy should be initiated/ reinitiated at low doses with slow titration. All patients at initiation or re-initiation of opioid therapy should be monitored in a fully equipped and staffed environment for at least 24 hours. Naloxone must be readily available.

Nursing staff should be educated about the unique monitoring requirements of patients being treated with ITDD.

Clinicians should familiarize themselves with the manufacturer's manual and with potential pump and catheter-related complications. Mechanical pump malformation is uncommon and has declined with each generation of pumps. Pump stalls invariably result in under-dosing which becomes evident clinically as decreased efficacy or withdrawal symptoms. Pump failure i.e. pump dislodgement, programme error, battery depletion and overfill errors. Incorrect refill may occur into the subcutaneous pocket with life threatening devastating consequences. Some pumps should be examined not less than 30 minutes after an MRI scan to ensure that the motor stall has re-started (Medtronic). Other pumps must be emptied prior to an MRI examination (Flowonix)

Catheters are the most vulnerable component of the system for damage or dislocation. Catheter complications include microfracture, leaks, disconnection, breakage, kinks, partial occlusion, inflammatory mass, catheter migration. The symptoms of catheter problems are manifested as reduced efficacy, increased pain, withdrawal symptoms and neurological dysfunction. The catheter may need to be revised, replaced or removed. Advances in catheter design and anchoring technique have reduced the incidence of catheter related complications.

Development of an inflammatory mass (granuloma) at the tip of the catheter remains one of the most serious risks of ITDD. If an inflammatory mass is suspected the diagnostic work-up should include a complete patient history, neurological examination and a TI weighted MRI performed with gadolinium.

Neurological complications may occur as a result of 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. Proper technique makes this complication uncommon than historical reports suggest.

Possible infections include meningitis, (bacterial, aseptic), catheter infections, implant site and wound infections.

Cerebrospinal fluid leaks, and post-dural puncture headaches have all been reported.

Guidelines should be in place to permit rapid access to neuroradiological expertise and neurosurgical treatment if neural compression is suspected. Surgical back-up should be arranged.

Emergency algorithms for the detection, investigation and management of complications should be in place to support the surveillance of suspicious symptoms

reported by the patient and their caregivers.

There must be clear pathways for dealing with complications, both in and out of hours. This will require agreed network arrangements. The patient's primary care team should be aware of potential complications, management plans, implanting team contacts and referral arrangements.

Issues with IT Pumps with persistaltic mechanism and Drug mixtures

Persistaltic mechanism of action involves a small piece of silicone inner tube and a rotating roller. This is used in the Medtronic pump. Medtronic has issued a warning on use of drug mixtures in their intrathecal Pumps. Use of unapproved drugs with SynchroMed pumps can result in an increased risk of permanent motor stall and cessation of drug infusion. Approved drugs for infusion therapy with the Medtronic Synchromed systems include morphine sulphate, morphine hydrochloride, floxuridine, methotrexate, baclofen or ziconotide in solution. Based on data from Medtronic's Implantable Systems Performance Registry (ISPR), the overall failure rate of the SynchroMed II pump at 78 months post implant is 2.4% when used to dispense approved drugs, and 7.0% when used to dispense unapproved drugs[23]. This risk should be balanced against the potential benefits of using drug mixtures i.e. better pain relief with improved side effect profile. This should be discussed with the patient.

9. Governance arrangements

Medical Leadership and MDT Composition

A minimum of two clinicians (usually FPMRCA) experienced in pain assessment and pain management. They must fully understand the indications, contraindications and perioperative management as well as all the potential interventions (medical, surgical, neuromodulation etc). They must be experienced in the management of intrathecal drug combinations. These clinicians must be led by at least one senior and experienced clinicians from the field with more than 5 years at consultant level. This team must be able to provide all the pain medicine related care needs of the patient throughout the process, including long term management of the ITDD (this care model may be shared care with local services).

Two clinicians able to undertake the interventional procedure (these may be the same FFPMRCA as above or neurosurgeons familiar with the technique working in collaboration with the above).

As well as the above, the ITDD MDT should include close and regular collaboration with psychology and pain physiotherapy. There should be access to endocrinology. The decision should be made with input from: the patient and relatives (informed and shared decision making), the patient's local services (primary care, etc), referring services (physician, surgeons, etc.) to ensure appropriate intervention and perioperative management, radiology.

A dedicated team of nurses, with a named nurse lead in the therapy should support,

co-ordinate and ensure compliance with therapy transitional requirements (such as patient information documentation, anticoagulation needs, drug changes, support of ward staff etc).

Experience of the pain consultants

As above: usually FFPMRCA, can demonstrate that they are experienced with assessing pain mechanisms and pain management in those with cancer and complex pain (e.g. have an established service, with proven track record of more than 5-10 implants per year for more than 5 years. For the new consultants: are a part of an established team with evidence of having trained in a multidisciplinary pain service that is experienced in the selection, implantation and maintenance of patients with ITDD. They must fully understand the indications, contraindications and perioperative management as well as all the potential interventions (medical, surgical, neuromodulation etc). They must be experienced in the management of medications and intrathecal drug combinations. These clinicians must be led by 1-2 senior and experienced clinicians from the field with more than 5 years at consultant level. New services would have to attract those lead consultants and ensure appropriate MDT training and involvement.

The team should be a part of a Specialised PMC (on site or Operational Delivery Networked through contract with such a PMC)

Number of staff: as above

Specialties on site

An experienced pain medicine consultant and experienced named pain nurse should be on site during working hours and the consultant available out of hours.

An experienced service, used to invasive procedures in complex patients, should provide 24 hour cover.

Close working relationships and defined plan should be available for neurosurgery, though they do not need to be onsite as neurosurgical emergencies are rare.

ITU must be onsite.

Many of the patients are disabled and by definition distressed because of pain. As a consequence the Team must be able to come to the patient and all investigations and interventions should be onsite.

Access: *to Neurosurgery*

The service must have established routine and emergency referral links to neurosurgery in the unlikely event of acute or chronic cord compression due to disease or granuloma. Rarely other complications such as development of pseudo-meningocoele may require neurosurgical referral.

Emergency plans

Each patient will have a management plan that should include information about access to the ITDD team. Patients should be given hand held records with clear

contact details for in and out of hours.

ITDD teams will ensure 24 hour access to advice and if required urgent out of hours action.

Emergency measure may require an A&E department and a hospital equipped with full critical care facilities including an intensive care unit.

Emergency plans

Once out of hospital, there should be an agreed patient care plan on how to manage patient and clinician concerns.

Implant trial

Format and duration of trial will depend on patient needs. An appropriate assessment needs to be undertaken as to nature of pain and current medication as well as other medical conditions and treatments. Prior to the trial the treatments should be optimised. For the duration of the trial, optimisation may involve drug changes, such as converting to shorter acting drugs and drug reductions.

The experienced clinician would undertake the trial after discussion with the team and having made decisions on optimisation of the patient and doses of trial drugs. The trial should involve fluoroscopy x-ray imaging and level of insertion takes in to account previous MRI/CT scan imaging discussed at a MDT.

The trial may be single shot or continuous infusion, epidural or intrathecal depending on patient requirements.

Post procedure the patient should be nursed in a facility experienced in managing intraspinal drug delivery.

Refills

Post ITDD implant, the initial titration of drugs will occur with direct involvement of the experienced Pain Management Consultants at the main centre. Once stabilised refills could be undertaken at agreed centres specifically trained and supported by the MDT. As the patient's condition progresses decisions about continued care would be agreed.

General Points

The infrastructure for ITDD is critical to reducing morbidity and mortality. This includes staffing, education and robust on-call arrangements with professionals trained and experienced both in the use and management of the implants and identification, investigation and management of complication of ITDDS. Much of that structure would be found in a specialised Pain Management Centre as defined in NHSE's Service Specification DO8.

The use of ITDD to treat intractable, chronic pain should be part of treatment algorithms for chronic, severe pain and should be considered only when there is failure of more conservative treatment measures or when unacceptable side-effects of high systemic opioid doses develop.

The treatment should be provided and directed by specialist MDTs in highly specialised Pain Management Centres. The specialist MDT is responsible for the organisation of follow-up arrangements that are safe and secure and that minimise morbidity and mortality. Causes of the later are largely avoidable and can be reduced by vigilance and team expertise in: careful patient evaluation, patient selection procedures, anaesthetic and surgical technique, trial of treatment, pump maintenance, refill procedures and patient follow-up with rapid recognition of complications and their appropriate treatment. Appropriate SOPs and protocols should be developed for the treatment of respiratory depression, initiation and re-initiation of analgesic drugs after revision/cessation of intrathecal therapy, with slow titration.

Policies for granuloma suspicion and management, endocrine insufficiency, under and overdose of drugs and pump and catheter malfunction should be prepared by each ITDD centre and shared with referring centre and primary care team.

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[xii]. Caution should be exercised on exceeding recommended doses, by the use of slow titration protocols.

It is the responsibility of the implanter and highly specialised pain management centre 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.

All future ITDD pump patients and devices for non-cancer pain should be included in the National Neuromodulation Registry.

10. Mechanism for funding

Intrathecal Pumps will be routinely funded, provided, this treatment is delivered in line with the Specialised Pain service specifications and the requirements of this policy. To date ITDD has been funded through local NHS arrangements by PCTs.

11. Audit requirements

Accurate measures of pain intensity and their impact on function and quality of life i.e. Brief Pain Inventory, VAS and pain interference scores, EQ5D-5L (quality of life measure, pain related health function and well-being), Patient's Global Impression of change, Drugs and concentration and doses pre procedure and as treatment is initiated and progresses i.e. at outcome measure points, Such measures serve as a baseline measurement from which to determine the continuing impact of therapy.

Frequency and type of complications both device and non - device related.

Number of patients assessed within three months of referrals for this treatment will be audited. Outcomes will be collected at 2 to 4 months initially and 9 to 12 months

post implant (as for SCS). Other clinical and service use indications as appropriate. The audit cycle is repeated after any surgical revision procedure.

12. Documents which have informed this policy

All relevant documents have been reference in the text and included in the references section.

13. Links to other policies

This policy follows the principles set out in the ethical framework that govern the commissioning of NHS healthcare and those policies dealing with the approach to experimental treatments and processes for the management of individual funding requests (IFR).

14. Date of review

This policy will be reviewed in April 2017 unless information is received which indicates that the proposed review date should be brought forward or delayed.

References

[i] Pert CB, Synder SH. Opioid receptor: demonstration in nervous tissue. Science1973; 179: 1947-9.

[ii] Yaksh TL, Rudy TA. Narcotic analgesia produced by a direct action on the spinal cord. Science1976; 192: 1357-8.

[iii] Cousins MJ, Mather LE, Glynn CJ, Wilson PR, Graham JR. Selective spinal analgesia. Lancet1979; 1: 1141-2.

[iv] Behar M, Magora F, Olshwang D, Davidson JT. Epidural morphine in treatment of pain. Lancet 1979; 1: 527-9.

[v] Wang J, Nauss LA, Thomas JE. Pain relief by intrathecally applied morphine in man. Anesthesiology 1979; 50: 149-51.

[vi] Gourlay GK, Cherry DA, Cousins MJ. Cephalad migration of morphine in CSF following lumbar epidural administration in patients with cancer pain. Pain1985; 23: 317-26.

[vii] Dickenson AH. Recent advances in the physiology and pharmacology of pain: plasticity and its implications for clinical analgesia. J Psychopharmacol1991; 5: 342-51

[viii] Rauck RL, Wallace MS, Burton AW, Kapural L, North JM.Intrathecal ziconotide for neuropathic pain: a review. Pain Pract. 2009 Sep-Oct;9(5):327-37

[ix] Collett B. et al: International Association for the Study of Pain Task Force on Wait-Times summary and recommendations. http://www.iasp-pain.org/AM/Template.cfm?Section=Wait_Times&Template=/CM/ContentDisplay.cfm&ContentID=13107

[11] Health survey England 2011, published December 20, 2012, available at http://www.hscic.gov.uk/catalogue/PUB09300 Chronic Pain chapter available at https://catalogue.ic.nhs.uk/publications/public-health/surveys/heal-surv-eng-2011/HSE2011-Ch9-Chronic-Pain.pdf

[12] Croft P, Blyth F, Van der Windt D. Chronic Pain Epidemiology. Oxford University press 2010

[13] Freburger J.K. et al. The rising prevalence of low back pain. Arch. Intern. Med. 2009.199:251-258

[14] Hayek SM, Deer TR, Pope JE et al. Intrathecal Therapy for Cancer and Non Cancer Pain. Pain Physician 201`;14:219-248.

[15] Falco FJ, Patel VB, Hayek SM, Deer TR, Geffert S, Zhu J, Onyewu O, Coubarous S, Smith HS, Manchikanti L. Intrathecal infusion systems for long-term management

of chronic non-cancer pain: an update of assessment of evidence. Pain Physician. 2013 Apr;16(2 Suppl):SE 185-216

[16] Raphael JH, Duarte RV, Southall JL, et al. BMJ Open 2013:3:e003061.

[17] van Rijn, MA. et al Intrathecal baclofen for dystonia of complex regional pain syndrome - Dose escalation study 2009 Pain 143(1-2): 41-47

[18] Duarte R. et al Long-term Intrathecal Drug Administration for Chronic Nonmalignant Pain. J Neurosurg Anesthesiol 2012;24:63–70

[19] Krishna K, Hunter G etal. Treatment of chronic pain by using intrathecal drug therapy compared with conventional pain therapies: a cost – effective analysis. J Neurosurg./Volume 97/ October, 2012

[20] Bolash R, Belinda U et al. Longevity and Cost of Implantable Intrathecal Drug Delivery Systems for chronic pain management: A retrospective analysis of 365 patients. Neuromodulation 2014 ; DOI: 10.111/ner 12235

[21] Gerhard MS, Hassenbusch SJ et al. Cost Effectiveness of Intrathecal Therapy for Pain. Neuromodulation, Volume 2, Number 2, 1999 77 -84

[22] Prager J, Deer T., Levy R., Bruel B., Buchser E., Caraway D., Cousins M., Jacobs M., McGlothlen G., Rauck R., Staats P., Stearns L. Best Practices for Intrathecal Drug Deliver for Pain. Neuromodulation 2013

[23] Medtronic urgent field safety notice on synchromed pump (FA553). Nov 2012. Accessed on line on 2nd June 2013 http://www.bfarm.de/SharedDocs/1_Downloads/EN/medDev/fca/01/2012/7002-12_Download_en.pdf?__blob=publicationFile

[24] http://www.britishpainsociety.org/book_useofmeds_professional.pdf accessed on line on 17th June, 2013

Appendix

Table 1. Algorithm for ITDD therapies in Neuropathic Pain (Published guidance on use of medications in ITDD (Polyanalgesic Consensus Conference 2012)

Line 1	Morphine	Ziconotide		Morphine + bupivacaine
Line 2	Hydromorphone	Hydromorphone+Bupivacaine or Hydromorphone+Clonidine		Morphine+Clonidine
Line 3	Clonidine	Ziconotide+Opioid	Fentanyl	Fentanyl+Bupivacaine or Fentanyl+Clonidine
Line 4	Opioid+Clonidine+Bupivacaine	Bupivacaine+Clonidine		
Line 5	Baclofen			

Table 2. Algorithm for ITDD therapies in Nociceptive Pain (Published guidance on use of medications in ITDD (Polyanalgesic Consensus Conference 2012)

Line 1	Morphine	Hydromorphone	Ziconotide	Fentanyl
Line 2	Morphine + Bupivacaine	Ziconotide+ Opioid	Hydromorphone+ Bupivacaine	Fentanyl + Bupivacaine
Line 3	Opioid + Clonidine			Sufentanil
Line 4	Opioid+Clonidine+ Bupivacaine		Sufentanil+Bupivacaine or Clonidine	
Line 5	Sufentanil + Bupivacaine + Clonidine			

Please note that the status of Ziconotide is not routinely commissioned but put forward as CtE

Table 3. Number of Pumps implanted per million population per annum in these countries

Pump type	Belgium	France	Holland	Germany	UK
Spasticity	34.6	1.72	4.5	13.12	9.7
Pain	18.3	-	1.5	figures not available	1.6