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Intrathecal Baclofen Pump for Spasticity

An Evidence-Based Analysis

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About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series.*

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To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and information from practicing medical experts and industry, adds important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to maximize patient outcomes.

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http://www.health.gov.on.ca/english/providers/program/ohtac/public_engage_overview.html

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Abbreviations/Acronyms

ABI	Acquired brain injury
ADL	Activities of daily living
AI	Ambulation index
BT	Botulinum toxin
CNS	Central nervous system
CP	Cerebral palsy
CSF	Cerebrospinal fluid
EDSS	Expanded disability status scale
ES	Effect size
FIM	Functional independence measure
GMFCS	Gross motor function classification system
GMFM	Gross motor function measure
HRQoL	Health related quality of life
HSCL	Hopkins symptom checklist
ISS	Incapacity status scale
MS	Multiple sclerosis
OT	Occupational therapy
QLI	Quality of life index
QoL	Quality of life
SCI	Spinal cord injury
SDR	Selective dorsal rhizotomy
SIP	Sickness impact profile

Executive Summary

Objective

To conduct an evidence-based analysis of the effectiveness and cost-effectiveness of intrathecal baclofen for spasticity.

The Technology

Spasticity is a motor disorder characterized by tight or stiff muscles that may interfere with voluntary muscle movements and is a problem for many patients with multiple sclerosis (MS), spinal cord injury (SCI), cerebral palsy (CP), and acquired brain injury (ABI).(1). Increased tone and spasm reduces mobility and independence, and interferes with activities of daily living, continence and sleep patterns. Spasticity may also be associated with significant pain or discomfort (e.g., due to poor fit in braces, footwear, or wheelchairs), skin breakdown, contractures, sleep disorders and difficulty in transfer.

Goals of treatment are to decrease spasticity in order to improve range of motion, facilitate movement, reduce energy expenditure and reduce risk of contractures. Existing treatments include physical therapy, oral medications, injections of phenol or botulinum toxin, or surgical intervention.

Baclofen is the oral drug most frequently prescribed for spasticity in cases of SCI and MS.(1) Baclofen is a muscle relaxant and antispasticity drug. In the brain, baclofen delivered orally has some supraspinal activity that may contribute to clinical side effects. The main adverse effects of oral baclofen include sedation, excessive weakness, dizziness, mental confusion, and somnolence.(2) The incidence of adverse effects is reported to range from 10% to 75%.(2) Ochs et al. estimated that approximately 25-30% of SCI and MS patients fail to respond to oral baclofen.(3;4)

Adverse effects appear to be dose-related and may be minimized by initiating treatment at a low dose and gradually titrating upwards.(2) Adverse effects usually appear at doses >60 mg/day.(2) The rate of treatment discontinuation due to intolerable adverse effects has generally been reported to range from 4% to 27%.(2)

When baclofen is administered orally, only a small portion of the original dose crosses the blood brain barrier and enters the central nervous system (CNS) fluid, which is the site of drug action. In order to bypass the oral route, baclofen may be administered intrathecally by infusion directly to the CNS.

Candidates for intrathecal baclofen infusion are patients with spasticity who have intractable spasticity uncontrolled by drug therapy, or who experience intolerable side effects from oral baclofen.

Advantages of intrathecal baclofen infusion are:

- Direct drug administration to the cerebrospinal fluid (CSF)
    - The central side effects of oral baclofen, such as drowsiness or confusion, appear to be minimized with intrathecal administration.
    - The intrathecal delivery of baclofen concentrates the drug in the CSF at higher levels than those attainable via the oral route.
    - Intrathecal administration can use concentrations of baclofen of less than one hundredth of those used orally.(5)

- Adjustable/programmable continuous infusion makes it possible to finely titrate patients' doses and to vary the doses over the hours of the day. For example, the dose can be relatively low to give the patients the extensor tone needed for ambulation during the day and increased at night, thereby improving quality of sleep.
- Reversible (in contrast to surgery).

A patient who is a candidate for intrathecal baclofen infusion must have no contraindications to the insertion of an intrathecal catheter (e.g., anticoagulant therapy, coagulopathy, local or systemic infection, anatomical abnormality of the spine).

Review Strategy

The Medical Advisory Secretariat reviewed the literature to assess the effectiveness, safety, and cost-effectiveness of intrathecal baclofen to treat patients who have intractable spasticity uncontrolled by drug therapy, or who experience intolerable side effects to oral baclofen.

The Medical Advisory Secretariat used its standard search strategy to retrieve international health technology assessments and English-language journal articles from selected databases.

Summary of Findings

- Level 2 evidence supports the effectiveness of intrathecal baclofen infusion for the short-term reduction of severe spasticity in patients who are unresponsive or cannot tolerate oral baclofen

- Level 3 evidence supports the effectiveness of intrathecal baclofen for the long-term reduction of severe spasticity in patients who are unresponsive or cannot tolerate oral baclofen

- Level 4 qualitative evidence demonstrates functional improvement for patients who are unresponsive or cannot tolerate oral baclofen

- Intrathecal baclofen is cost-effective with costs which may or may not be avoided in the Ontario health system

- True functional use remains to be determined

Objective

To conduct an evidence-based analysis of the effectiveness and cost-effectiveness of intrathecal baclofen for spasticity.

Background

Clinical Need: Target Population and Condition

Spasticity is a motor disorder characterized by tight or stiff muscles that may interfere with voluntary muscle movements and is a problem for many patients with multiple sclerosis (MS), spinal cord injury (SCI), cerebral palsy (CP), and acquired brain injury (ABI).(1) Increased tone and spasm reduce mobility and independence and interfere with activities of daily living, continence and sleep patterns. Spasticity may also be associated with significant pain or discomfort (e.g., due to poor fit in braces, footwear, or wheelchairs), skin breakdown, contractures, sleep disorders and difficulty in transfers.(1)

Spasticity develops gradually after the initial insult to the central nervous system (CNS). It usually becomes noticeable in the first few months but the timing can vary depending on the underlying neurologic insult. Once recovery from the neurologic deficit stabilizes, the spasticity also tends to stabilize.

Spasticity is not always detrimental. Spasticity provides posture and tone to a limb that can assist with weight bearing, even if the patient cannot walk. However, excessive tone may also interfere with activities. Therefore, it is only when spasticity interferes with function or puts the patient at risk of hurting himself or herself that it needs to be treated.

Spasticity can be aggravated by noxious stimuli that increase the afferent input (incoming nerve message to the CNS) on the stretch reflex. These stimuli include: urinary tract infections, constipation, ingrown toenails, pressure ulcers and poor fit in a brace or wheelchair. Such factors should be examined before initiating treatment.

The estimated incidence of these conditions is shown below:

Multiple Sclerosis
MS is an inflammatory disease that results in myelin loss in the CNS, with secondary axonal loss. This leads to the development of plaques in the brain and spinal cord. The etiology is unknown, however, it is hypothesized that MS is the result of an autoimmune response.

The clinical pattern is variable in severity and is unpredictable.(3) People with MS develop a range of symptoms including fatigue, memory and attention difficulties, bowel and bladder problems, weakness, pain and increased muscle stiffness (increased tone or spasticity). Approximately one third of MS patients will require assistance to walk or be dependent within 15 years of diagnosis.(3)

The prevalence of MS in the United Kingdom (UK) is approximately 100 per 100,000. In Canada, the prevalence of MS is approximately 100-200 per 100,000.

Cerebral Palsy

CP is a motor disorder appearing before the age of 3 years due to non-progressive damage to the brain. Cerebral palsy occurs in 2-3/1000 children.(3) CP is a heterogenous condition, but 80-90% of cases will have spasticity, which usually affects at least one lower limb.(6)

Quadriplegia (loss of movement and sensation in both the arms and legs) accounts for approximately 7% of CP.

Patients with diplegic CP (loss of movement and sensation in corresponding limbs on both sides of the body) account for 44% of those with CP, and are usually able to walk with aids.(3) Around the age of 8 years, however, their mobility fails to improve, leading in some cases to wheelchair confinement.(3) This is due to an increasing mismatch between weight and strength as well as muscle contractures developing as a result of spasticity. Orthopedic surgery is needed for contractures to elongate the muscle at the tendons and increasingly all muscles are operated upon together.(3)

Spinal Cord Injury/Acquired Brain Injury

Spinal cord injury occurs as a result of motor vehicle accidents, violence, falls, diving accidents and work or sports related injuries. Approximately 55% of SCI patients will be affected by paraplegia (loss of movement and sensation in the lower body) while 44% are affected by quadriplegia (loss of movement and sensation in both the arms and legs).

Spasticity is reported to develop within one year of injury in 67% of patients; 37% receive antispastic medication and 11% fail to respond to the treatment.(3;7) Sampson estimated that approximately 5% to10% of SCI patients will require intrathecal drug delivery systems to treat excessive spasticity.(3)

Acquired brain injury due to hypoxic brain injury or trauma is a further cause of cerebral spasticity.(3) The proportion of patients who have severe intractable spasticity uncontrolled by drug therapy has not been reported in the literature. The London Health Sciences Centre Business Plan reported that the number of treatable patients with spasticity associated with ABI is rare.

Clinical Scoring Systems to Assess Spasticity

Two commonly used and validated clinical scoring systems to assess spasticity include the Ashworth scale (Table 1) and the spasm frequency or reflex scale (Table 2).(4)

Table 1: Ashworth Scale

Grade	Degree of Muscle Tone
1	No increase in tone
2	Slight increase in tone, giving a "catch" when affected part is moved in flexion or extension
3	More marked increase in tone, but affected part easily flexed
4	Considerable increase in tone; passive movement difficult
5	Affected part rigid in flexion or extension

Table reprinted with permission from Harvey Whitney Books; Lewis KS, Mueller WM. Intrathecal baclofen for severe spasticity secondary to spinal cord injury. Ann Pharmacother 1993; 27:767-774

Table 2: Reflex Scale

Score	Reflex Response
0	No response
1	Hyporeflexia
2	Normal response
3	Mild hyperreflexia
4	4 beats clonus
5	Unsustained clonus, >4 beats
6	Sustained clonus

Table 2 reprinted with permission from Harvey Whitney Books; Lewis KS, Mueller WM. Intrathecal baclofen for severe spasticity secondary to spinal cord injury. Ann Pharmacother 1993; 27:767-774

Existing Treatments Other Than Technology Being Reviewed

Goals of Treatment

Decrease spasticity to improve range of motion
Decrease pain
Facilitate movement
Reduce energy expenditure
Reduce risk of contractures

Physical Therapy

Patients and caregivers are taught to avoid certain postures and noxious or external stimuli that promote or exacerbate spasticity.(1) Regular stretching is important to prevent contractures and to maintain the range of movement. Braces may be used to maintain a spastic limb in a reflex-inhibiting posture and prevent contractures.(1)

Oral Medications

Randomized controlled trials (RCTs) have reported antispasticity medications to be efficacious in the management of spasticity, especially in adults with spinal disorders (e.g., SCI and MS).(1) Their efficacy in cerebral disorders (ABI, stroke, CP) is less studied in adults and especially in children. The medications commonly used are baclofen, dantrolene, tizanidine, gabapentin, and benzodiazepines.(1;3) Many antispasticity oral drug trials have been conducted in adults with spastic disorders, with relatively few trials done in children.(8;9)

In 2004 Montane et al. conducted a systematic review of oral antispastic drugs in nonprogressive neurologic diseases.(10) Twelve randomized controlled trials (RCTs) (N=469 patients) were included (6 on stroke, 3 on spinal cord diseases, and 3 on CP). The patients with CP were all children (n=67). Tizanidine was assessed in 4 trials (276 patients, 142 exposed), dantrolene in 4 (103 patients, 93 exposed), baclofen in 3 trials (70 patients, 55 exposed), diazepam in 2 trials (127 patients, 76 exposed), and gabapentin in one trial (28 patients, all exposed).(10) Only one trial investigating the use of oral baclofen in children (N=20) with CP was identified.(11)

Most of the trials had small sample sizes, and were of short duration with inadequate methodologic quality.(10) Sample size calculations were not reported in any trial. Ten trials were controlled with placebo and 2 were direct comparisons between drugs. Efficacy outcomes of interest were variable among the studies. Four trials described the magnitude of the antispastic effect. Adverse effects were generally more frequent in the active treatment groups (range 25% to 91%) than in the placebo groups (range 0% to 53%). Baclofen was associated with sedation, dizziness and muscle weakness (range of adverse events of 25 to 27% of patients).(10)

Montane et al. concluded that the evidence on the efficacy of oral antispastic drugs in nonprogressive neurologic diseases is weak, and does not include evaluation of patients' quality of life (QoL).(10)

Baclofen is the oral drug most frequently prescribed for spasticity in cases of SCI and MS.(1) Baclofen is a muscle relaxant and antispasticity drug that is a structural analogue of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Baclofen binds to presynaptic GABA-B receptors within the brain stem, dorsal horn of the spinal cord and other CNS sites. In the brain, baclofen delivered orally has some supraspinal activity that may contribute to clinical side effects. The main adverse effects of oral baclofen include sedation, excessive weakness, dizziness, mental confusion, and somnolence.(2) The incidence of adverse effects is reported to range from 10% to 75%.(2) Ochs et al. estimated that approximately 25%-30% of SCI and MS patients fail to respond to oral baclofen.(3;4)

Adverse effects appear to be dose-related and may be minimized by initiating treatment at a low dose and gradually titrating upwards.(2) Adverse effects usually appear at doses >60 mg/day.(2) The rate of treatment discontinuation due to intolerable adverse effects has generally been reported to range from 4% to 27%.(2)

When baclofen is administered orally, only a small portion of the original dose crosses the blood brain barrier and enters the CNS fluid, which is the site of drug action. In order to bypass the oral route, baclofen may be administered intrathecally by infusion directly to CNS.

Injections of Phenol or Botulinum Toxin

Focal treatment of spastic muscles has been used in people with cerebral spasticity.(1) The goal is to block the final common nerve pathway. Phenol injections have been used to block large nerves going to specific regions of the body that are spastic.(1) Complications of phenol injections that have been reported include pain, peripheral edema, skin sloughing and wound infection.(1)

Botulinum toxin type A injections have been used to block the neuromuscular junction with resultant weakness (reduction of muscle tone).(1) There is a maximal total dose according to body weight for each course of treatment, beyond which the toxin escapes into the systemic circulation in significant amounts to cause general fatigue. Due to the limited amount that can be given safely at one time, only a small number of muscles can be treated every 4-6 months. Limited muscle pain, bruising and transient fever may occur on the day of the injection.

The major indications for botulinum toxin include the relief of spasticity in the calves in children with hemiplegic CP (loss of movement and sensation in the right or left half of the body) and the calves, hamstrings and hip adductors in diplegics.(3) Botulinum can also be used in patients with quadriplegia, particularly in the hip adductors. However, it is not usually considered for SCI patients since the treatment is not appropriate in generalized spasticity.

Surgical Intervention

Due to the invasiveness of the procedure, surgical treatment of spasticity is reserved for the most refractory cases.(1)

Selective dorsal rhizotomy (SDR) of the lumbrosacral nerves is a neurosurgical procedure designed by Fasano et al. in 1978 to treat spasticity in the lower extremities of children with CP.(12) The surgery requires testing individual sensory nerve rootlets to determine those rootlets that when stimulated, produce abnormal electrophysiologic responses. Rootlets producing abnormal responses are cut and normal responding rootlets are spared.

Other surgical procedures include myelotomy (incision of the spinal cord) and cordotomy or cordectomy (excision of part of the cord).(1) Many orthopedic procedures such as lengthening, releasing or transferring a tendon, may be helpful in optimizing function and preventing contractures.(1) Osteotomies (cutting of bone) may be undertaken to correct deformity.

New Technology Being Reviewed

Intrathecal Baclofen Pump

Candidates for intrathecal baclofen infusion are patients with spasticity who have intractable spasticity uncontrolled by drug therapy or who experience intolerable side effects to oral baclofen.

Test Procedure

Before implantation, a bolus dose of baclofen is injected into the CSF using a lumbar puncture or a temporary catheter, under local anesthesia, to screen for a patient response to treatment. The dose of baclofen is titrated upwards in 25 microgram per day aliquots until an approximately 4 to 8 hour response is observed. If the patient does not respond to 100 micrograms intrathecally, the patient is considered to have an inadequate response and should not undergo implantation.

Creedon et al. stated that generally, patients considered as candidates for pump implantation are those that have decreased spasticity, as indicated by a 2 point or more decrease in their Ashworth or Penn spasm scale scores, for a period of 4-8 hours after the bolus injection.(13) Some patients do not have any response; others do not respond substantially enough to justify implantation. A few patients who have adequate reduction in spasticity from intrathecal administration decline implantation because muscle tone they used for functional activities was lower during the trial than prior to trial.(13)

Pump Implantation

An intrathecal pump delivers baclofen directly into the CSF. The system consists of a catheter and a pump (Appendix 1). The pump is surgically placed under the skin of the abdomen near the waistline, under general anesthesia. The pump stores and releases prescribed amounts of medication through the catheter. The pump is refilled by inserting a needle through the skin into a filling port in the centre of the pump.

Pumps can be programmable or nonprogrammable. Using an external programmer, a physician can make adjustments in the dose, rate and timing. The pump reservoir can be refilled approximately every 2-3 months by percutaneous injection. The pump is taken out and replaced at the end of the battery's life span (approximately 5-7 years).

Length of Treatment

The length of time that the treatment will be administered depends upon the nature of the underlying disease. For a progressive disease (e.g., MS), the length of time intrathecal baclofen infusion may be beneficial will be dependent upon the progression of the disease. For other conditions such as SCI or CP, where progression does not affect the spasticity, there is no defined limit as to how long the treatment may be required and there are no firm recommendations for tolerance management. Drug holidays have been reported as an approach to the management of tolerance. (13)

Due to limited battery life, the initial pump procedure will need to be repeated every 5-7 years. The dosage of baclofen may be increased due to increased tolerance of the drug.

Advantages of intrathecal baclofen infusion are:

- Direct drug administration to the CSF:
    - The central side effects of oral baclofen such as drowsiness or confusion appear to be minimized with intrathecal administration.
    - The intrathecal delivery of baclofen concentrates the drug in the CSF at higher levels than those attainable via the oral route.
    - Intrathecal administration can use concentrations of baclofen of less than one hundredth of those used orally.(5)
- Adjustable/programmable continuous infusion makes it possible to finely titrate patients' doses and to vary the doses over the hours of the day. For example, the dose can be relatively low to give the patients the extensor tone needed for ambulation during the day, and increased at night, thereby improving quality of sleep.
- Reversible (in contrast to surgery).

A patient who is a candidate for intrathecal baclofen infusion must have no contraindications to the insertion of an intrathecal catheter (e.g., anticoagulant therapy, coagulopathy, local or systemic infection, anatomical abnormality of the spine).

Sampson et al.(3) reported the estimated incidence and prevalence of spasticity in conditions potentially amenable to treatment with intrathecal baclofen infusion. Assuming an Ontario population of 12 million, the following prevalent and incident cases in Ontario are estimated in Table 3.

The estimated prevalence and incidence of SCI, CP and MS from the literature is shown in Table 3.

Table 3: Estimated prevalence and incidence of SCI, CP and MS from the literature

Condition	Incidence per 100,000 per year	Prevalence per 100,000
SCI	1.7	72
CP	2.6	50
MS	3-7	100-200

According to Sampson et al., in 1998, approximately 200 patients in Britain were implanted with pumps for intrathecal baclofen.(3) Approximately 60% were SCI patients, 30% had MS and the remaining 10% of patients had an underlying cause of spasticity due to other causes such as CP, traumatic brain injury and metabolic disorders.(3)

Regulatory Status

The following products are licensed by Health Canada as Class 3 devices for intrathecal baclofen infusion:

- Synchromed EL System®, Synchromed System®, Medtronic Inc. (License # 7444, and 934 respectively).
- Constant Flow M3000 Series Implantable Infusion Pump®, Codman & Shurtleff Inc. (License # 12699).

- Infusaid Constant Flow Implantable Infusion Pump, Codman & Shurtleff Inc. (License # 14493).
- Archimedes Implantable Infusion Pump®, Codman Neuro Sciences Sarl, A Johnson & Johnson Company, (License # 61965).

According to the 2005 Compendium of Pharmaceuticals and Specialties, the indications for intrathecal baclofen are:

> *"For the management of patients with severe spasticity due to spinal cord injury or multiple sclerosis who are unresponsive to oral baclofen or who experience unacceptable side effects at effective oral doses."*(14)

In July 2002, Health Canada posted drug safety information regarding Lioresal intrathecal (baclofen).(15) The notice provided updated information to include warnings about rate cases of intrathecal baclofen withdrawal that can lead to life-threatening sequelae and/or death in patients who abruptly discontinue therapy.(15)

At the time of the Health Canada posting, Lioresal Intrathecal was indicated for the management of patients with severe spasticity due to spinal cord injury or multiple sclerosis who are unresponsive to oral baclofen or who experience unacceptable side effects at effective oral doses.(15)

The following box warning was added to the Lioresal intrathecal product monograph:

> *"Abrupt discontinuation of intrathecal baclofen, regardless of the cause, has resulted in sequelae that include high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity, that in rare cases has advanced to rhabdomyolysis, multiple organ-system failure and death.*
>
> *Prevention of abrupt discontinuation of intrathecal baclofen requires careful attention to proper programming and monitoring of the infusion system, refill scheduling and procedures, and pump alarms. Patients and caregivers should be advised of the importance of keeping scheduled refill visits and should be educated on the early symptoms of baclofen withdrawal. Special attention should be given to patients at apparent risk (e.g. spinal cord injuries at T-6 or above, communication difficulties, history of withdrawal symptoms from oral or intrathecal baclofen). Consult the technical manual of the implantable infusion system for additional postimplant clinician and patient information. (see WARNINGS)."(15)*

Lioresal® Intrathecal was approved for the treatment of cerebral spasticity by the United States Food and Drug Administration (FDA) in June 1996. Children must be at least 4 years of age and large enough to accommodate the implanted pump. Prior to 1996, intrathecal baclofen was FDA-approved for spasticity due to SCI and MS.

Literature Review on Effectiveness

Objective

The Medical Advisory Secretariat did a literature review to assess the effectiveness, safety, and cost-effectiveness of intrathecal baclofen to treat spasticity.

Questions Asked

- Does intrathecal baclofen improve gait, activities of daily living and hygiene?
- Does intrathecal baclofen decrease spasm frequency?
- Does intrathecal baclofen defer time to orthopedic surgery?

Methods

Inclusion criteria

English-language articles (April 2003 – 2004)
Journal articles that reported primary data on the effectiveness or cost-effectiveness of data obtained in a clinical setting, or analysis of primary data maintained in registries or databases
Study design and methods that were clearly described
Systematic reviews, randomized controlled trials (RCTs), non-RCTS or cohort studies that had $\geq$20 patients, and cost-effectiveness studies

Exclusion criteria

Duplicate publications (superseded by another publication by the same investigator group, with the same objective and dataNon-English-Language articles
Non-systematic reviews, letters and editorials
Animal and in-vitro studies
Case reports
Studies that did not examine the outcomes of interest

Interventions

Intrathecal baclofen infusion
Controls underwent optimal conventional management

Literature Search

Cochrane database of systematic reviews
ACP Journal Club
DARE
INAHTA
EMBASE
MEDLINE
Reference sections from reviews and extracted articles

Outcomes of Interest

Reduction of spasticity
Activities of daily living

QoL
Adverse effects
Economic analysis data

Results of Literature Review for Intrathecal Baclofen for Spasticity

Summary of Existing Health Technology Assessments

Six international health technology assessments were identified in the literature search. The most recent assessment was conducted by the Australian Safety and Efficacy Register of New Interventional Procedures-Surgical (ASERNIP-S) in May 2003. ASERNIP-S did not report finding a previously conducted meta-analysis from 1997 by Creedon et al.(13) in their literature search (reason not stated). ASERNIP-S also stated that the systematic review by Taricco et al.(16) (discussed later in this document) was not included in their analysis (reason not stated).

Another HTA by Sampson et al.(3) from the Trent Institute for Health Services Research published in 2000, and fully discussed later in this document, reported on and analyzed the meta-analysis by Creedon et al.(13) A review and commentary of the meta-analysis by Creedon et al. from the Trent Institute for Health Services Research report is provided below.

Foundation of Most International HTAs: Meta-analysis of Intrathecal Baclofen (Creedon et al., 1997)(13)

Creedon et al. (13) conducted a meta-analysis of English-language trials of intrathecal baclofen infusion that were published prior to June 1996. In total, 27 studies were included (N=490 patients; n=206 SCI patients; n=162 MS patients; n=59 CP patients; n=64 patients with other causes of spasticity). Patients had spasticity resistant to oral medication. The average patient in the meta-analysis was 36 years old, 7 years post-onset of the CNS disorder, and had undergone followup evaluations for 18 months after implantation of the pump.(3)

Overall results indicated that:

- 91% of patients who were screened had a positive response to screening
- 92% of patients who had a pump implanted had a positive response to the pump;
- 92% of patients who had a pump implanted were still using the pump at one-year followup.

The overall effect on the Ashworth and spasm scores, and the effect in different patient groups is shown in Table 4.

Table 4: Effect of intrathecal baclofen on Ashworth and spasm

Condition	Mean Ashworth Score pre intrathecal baclofen	Mean Ashworth Score post intrathecal baclofen	N*	P value	Mean Spasm Score pre intrathecal baclofen	Mean Spasm Score post intrathecal baclofen	N*	P value
All patients	3.9	1.6	134	<0.001	3.2	0.6	51	<0.001
MS	4.2	1.3	43	<0.001	3.2	0.4	18	<0.001
CP	2.9	2.0	23	0.34	-	-	0	-
SCI	4.0	1.7	49	<0.001	3.4	0.8	21	<0.001
Other	4.3	1.7	19	<0.001	3.2	0.8	11	<0.001

*Number of patients on which estimate is based.

Table reprinted with permission; From Sampson FC, Hayward A, Evans G, Touch S, Morton R, Vloeburghs M et al. The effectiveness of intrathecal baclofen in the management of patients with severe spasticity. 2000. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield. Guidance Note for Purchasers: 00/01

The effect on spasticity in CP patients was less marked than in other patients possibly because the meta-analysis did not include many patients with CP, and these patients had less severe spasticity at baseline than other patients.

The dosage of baclofen required to achieve spasticity reduction increased during followup. The average starting dose was around 150 micrograms per day and after 16 months, this increased by approximately 250%.(3)

Summary of International Health Technology Assessments

Australian Safety and Efficacy Register of New Interventional Procedures-Surgical (ASERNIP-S), Australia, 2003

A detailed summary of the 2003 ASERNIP-S report is provided below.

A literature search was conducted up to April 2003. In total, 53 studies of intrathecal baclofen infusion were identified. Seven RCTs were excluded from the analysis because "they were internal comparisons assessing the efficacy of intrathecal baclofen (for spasticity or dystonia) to intrathecal saline (studies were usually of double blind, crossover design, followed with an observational study of intrathecal baclofen)."(17) Forty-four case series/case reports were also excluded. In the end, 2 case series studies were included "with regard to patient numbers and length of followup to present a snapshot of safety and efficacy".

Study characteristics of these 2 case series are presented in Table 5.

Table 5: Characteristics of case series studies included in ASERNIP-S assessment

Author	Intervention	Study Design	Study Population	Inclusion/Exclusion Criteria
Ordia et al., 2002 USA	**Screening Trial** Bolus injection of intrathecal baclofen given by lumbar puncture or via intrathecal catheter A double-blind randomized placebo controlled trial was performed on the first 9 patients; placebo (saline) and 50ug baclofen were randomly given on day 1 and day 2. If there was no response to the baclofen, placebo and 75 ug of baclofen were given on days 3 and 4. Nonresponders were randomized to placebo and 100 ug baclofen on days 5 and 6.) A reduction in the mean Ashworth Score or the mean Spasm Frequency Score for at least 4 hours was considered to b a positive response. 57 patients were enrolled into an open label treatment protocol without placebo. The final 86 patients were treated following FDA approval, also screened without placebo. **Pump** Synchromed Infusion System. Investigators left an interval of several days between screening and implantation to allow the dura to heal and potentially to reduce the risk of infection).	Case Series Followup: Mean 73 months (range 2-137) Loss to Followup: Not specifically stated but 8/131 (6%) pumps were explanted as patients withdrew from intrathecal therapy. Study Period: Not stated	Sample Size: 131 patients (152 patients screened) Age: Mean 42 years (range 17-73) Intractable spasticity of spinal cord origin: 63/131 (48%) spinal and supraspinal multiple sclerosis 53/131 (40%) spinal cord injury 15/131 (12%) other including: familial spastic paraparesis lateral sclerosis cervical spondylotic myelopathy spinal cord tumour transverse myelitis syringomyelia spinal epidural abscess spinocerebellar degeneration adrenal leukodystrophy 90/131 (69%) quadriplegic 41/131 (31%) paraplegic 109/131 (83%) nonambulatory 22/131 (17%) ambulatory Mean duration of symptoms 14 years (5 months-34 years) Prior medication use Average daily dose of oral baclofen, 106 mg. For patients on diazepam and tizanidine, average daily doses of baclofen were 26 mg and 21 mg. Outcome measures and validity: Ashworth Scale: 1 to 5 (“no increase in tone” to “affected part(s) rigid in flexion or extension”) Spasm Frequency Score:	Inclusion Criteria: Patients interviewed and examined to determine suitability. Eligible if patients had a mean Ashworth Score of at least 3 and a Spasm Frequency Score of at least 2 in the affected limb. Exclusion Criteria: Pregnant or of childbearing potential and were not using birth control, patients with a history of allergy to baclofen, patients with severely impaired renal or hepatic function.

			0 to 4 (“none” to “greater than 10 spontaneous spasms per hour”) Spasticity considered severe if Ashworth Score was ≥3 or the Spasm Frequency Score ws ≥2.	
Stampien and Tsai, 2000 USA	**Screening Trial** Screened by test dose via lumbar puncture with the majority performed with 50ug boluses. 853/978 (87%) reported test doses were successful. **Pump** SynchroMed. 936 pumps placed.	Case series Followup: Not stated Loss to followup Not applicable – survey of centres Study Period Summer 1998, clinical survey Operator Details 17 children’s hospitals 15 general hospitals 7 rehabilitation hospitals 1 outpatient facility	Sample Size Clinical survey of 115 centres. 40/115 (35%) returned the survey 936 pumps had been placed and 1002 test doses completed. Age Not stated Spasticity Spasticity reported for 770 patients 336/770 (44%) cerebral palsy 168/770 (22%) spinal cord injury 21/770 (3%) anoxic encephalopathy 73/770 (9%) traumatic brain injury 6/770 (1%) stroke 166/770 (21%) “other” Baseline medication use Not stated Outcome measures and validity Not stated	Inclusion Criteria Centres currently providing intrathecal baclofen pumps Exclusion Criteria Not stated

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Safety results from the 2 case series are shown in Table 6.

Table 6: Safety results from case series in the assessment by ASERNIP-S

Complications	Ordia et al. 2002 N=152	Stempien and Tsai, 2000 N=936
Mortality	10/131 (8%) Not attributable to CIBI	-
Drug Related		
Constipation	12/131 (9%) patients with preexisting constipation but required a more intense bowel regimen after surgery	2.9% following implantation
Hypotension and bradycardia	2/131 (2%)	12/978 (1%) screening dose - hypotension 0.9% following implantation – hypotension
Muscular hypotonia	7/131 (5%)	-
Nausea, vomiting, dizziness, drowsiness/lethargy/fatigue	1/131 (0.8%) nausea, dizziness, drowsiness	26/978 (3%) screening dose – nausea, vomiting
Sedation	-	22/978 (2%) screening dose
Seizures	-	3/978 (0.3%) screening dose 1/936 (0.1%) after initial hospitalization
Tolerance	2/131 (1.5%) Patients weaned and kept off baclofen for a 4-6 week drug holiday but received intrathecal morphine. When baclofen was restarted, the effective dose was less than half of which the patients were tolerant to and patients stayed on low dose for 3-4 months before an increase was needed.	-
Urinary retention/hesitancy/disturbances	4/131 (3%)	16/978 (1.5%) screening dose – 1 case of retention Following implantation – 2 cases retention
Pump Related		
Flipped pump	2/131 (1.5%)	1 case following implantation
Stuck valve	1/131 (0.8%)	-
Replacement/revision/repositioning	-	At the time of survey 66/936 (77%) pumps had been replaced. Reasons were: 16/936 (1.7%) infection 12/936 (1%) battery failure 11/936 (1%) patient request 8/936 (0.9%) hypermobility with effusion 4/936 (0.4%) pump failure 2/936 (0.2%) CSF leak 1/936 (0.1%) dehiscence 1/936 (0.1%) smaller pump placed 11/936 (1%) not stated
Explantation	8/131 (6%) patients withdrew from therapy	
Catheter related	24 catheter related problems in 19 patients. All but 2 occurred with earlier models of the catheter	
Breaks	8/131 (6%)	-
Dislodgement	2/131 (1.5%)	-
Occlusion/obstruction/kink	12/131 (9%)	-
Punctures	2/131 (1.5%)	-
Replacement/revision/repositioning	-	At the time of survey: 64/936 (7%) catheters

		had been replaced. Reasons were: 40/936 (4%) kinks or migration 3/936 (0.3%) infection 1/936 (0.1%) occlusion 1/936 (0.1%) arachnoiditis 19/936 (2%) not stated
Wound problems		
Pocket erosion	2/131 (1.5%)	
Pocket infection	1/131 (0.8%) superficial	
Other		
CSF leak/collection	1/131 (0.8%) treated with laminectomy and dural repair	2.2% following implantation – leak 3.3% following implantation – collection 8/936 (0.9%) after initial hospitalization – collection
Hematoma		0.8% following implantation
Hydrocephalus		1 case following implantation 2/936 (0.2%) after initial hospitalization
Infection		1.5% following implantation 16/936 (1.7%) after initial hospitalization
Meningitis	1/131 (0.8%) bacterial meningitis developed one week after occluded catheter replaced. Entire hardware removed and patients treated with intravenous antibiotics.	
Spinal type/subdural puncture headache		
Following screening trials	10/152 (7%)	<1% was stated in text as "headache"
Following implantation	6/131 (5%) 2/6 did not resolve with bed rest and were treated with autologous epidural blood patch	2.4% was stated in text as "headache"
Worsened gait	-	1 case following implantation

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Efficacy results from the **2 case series** are shown in Table 7.

Table 7: Efficacy results from the 2 case series studies

Efficacy Endpoint	Ordia et al. 2002 N=152	Stempien and Tsai, 2000 N=936
Ambulatory ability	2/109 (2%) who were nonambulatory were able to walk.	-
Ashworth Score	Decrease, mean 4.2 to 1.3 ($p<0.0005$)	-
Dose escalation	Average daily dose was 134 ug which increased to 247 ug at 6 months and 277 ug at 12 months. (Dose was stable for spinal cord injury patients at 12 months but continued to escalate in multiple sclerosis patients, probably due to progression of the disease).	After 6 months: Lowest daily dose was 25 ug/day Highest daily dose was 1500 ug/day
Driving ability	4/131 (3%) could drive (not able to drive before using the pump)	
Gait and balance	Improved for 18/22 (82%) ambulatory patients	
Length of stay after implantation		Average 2-3 days
Spasm frequency score	Mean pre pump 3.4 to post pump	

	0.6	
Urodynamic parameters	8 patients had reduced detrusor hyperreflexia and a bladder sphincter dyssynergy and increased bladder capacity. Some patients (n=?) converted from an indwelling catheter to intermittent drainage, and others (n=?) required fewer daily catheterizations.	
Work status	Control of spasticity allowed a number of patients (n=?) to work or take less sick time.	
Miscellaneous comments		>90% **of centres** reported improvements in areas of daily care 97% reported easier diapering 95% improved transfers 95% improved sitting tolerance 94% easier dressing 94% improved orthotic wear 90% improved dexterity 85% improved contractures 81% improved respiratory function 74% improved ambulation endurance 57% better swallowing function; 1% worse 50% better for drooling, 23% worse 57% better head control, 23% worse 68% better bladder control, 0.5% worse 40% better bowel control, 27% worse

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ASERNIP-S (17) concluded:

> *"Infusion of baclofen for treatment of spasticity intrathecally via implantable infusion devices appears effective for patients who have been screened for response to intrathecal medication prior to implantation. This method of treating spasticity appears safe, although drug related complications do occur (similar with systemic or parenteral drugs) but device related complications (such as catheter related complications) can also occur which may result in surgical revision or removal of the device. Treatment of spasticity via intrathecal baclofen may be less costly than medical management in the long term."*

National Health Service Research & Development (NHS R&D) United Kingdom, 2003

Beard et al.(18) addressed 2 general questions for NHS R&D:

- What are the treatments currently available for the management of spasticity and pain in MS?
- What is the clinical and cost-effectiveness of each of these treatments for spasticity and pain in MS?

NHS R&D stated that the purpose of the report was to provide a wider perspective of the needs and potential interventions in MS. It was not possible to cover each individual treatment in great depth. The report did not look at treatments other than drug therapy.

A literature search was conducted up to July 2000. It was reported that searches were repeated in March

2002.

Quantity of Research
Twenty studies evaluating the use of intrathecal baclofen were identified. Five were excluded because the number of patients with MS was less than 50% of the total; the results for this group of patients were not presented separately. Fifteen studies were included in the review. Four studies came from the same centre and it was not clear to what extent the patients were included in more than one of them.

One study was a double-blind RCT lasting 13 weeks.(19) Another was a short-term (3 days) crossover RCT conducted in 1989.(20) In 1993, Coffey et al. used a double-blind randomized technique in the initial screening to assess initial response to a bolus dose before recruiting subjects into the open-label uncontrolled studies.(21) The remaining 12 studies were longitudinal, open label, uncontrolled designs or case series.

Beard et al. (18) stated that it is unfortunate but understandable given the complex nature of the intervention that there was only one longer term double-blind RCT.(18) However, researchers may be either unable or unwilling to randomize or blind patients.(18) Use of a double-blind RCT is unlikely for this treatment in patients with MS because of the invasive nature of the intervention, possible ethical issues, the need to titrate dosage over time and the large number of treatment-related complications. Despite the potential for bias arising from the uncontrolled studies, Beard et al. included them because of the lack of other evidence. The duration of treatment in the studies ranged from 4 months to 6 years.

Populations Examined
None of the studies were restricted to patients with MS. However, in all included studies, >50% of the patients had MS or the results for the MS patients were shown separately. In all 15 studies, all patients had severe spasticity and in 6 studies the patients were stated explicitly to be unresponsive to oral therapy. In most of the studies, the patients were nonambulatory and most had had their condition for a long time.

Intervention
All studies examined the effect of baclofen administered intrathecally by a programmable continuous infusion pump. Most of the studies used an initial screening stage in which baclofen was administered as a bolus dose to test the responsiveness of the patient. If this was successful, a pump and catheter were then inserted from the administration of baclofen on a long-term basis. The long-term dosage used in these selected studies ranged from 21 to 648 ug per day.

Outcomes Measured
Several different outcome measures were used. The main ones were the Ashworth scale and various spasm frequency scales.

Validity of Studies
The longitudinal studies and case series relied on the observation of the patient's condition prior to implantation of the pumps as controls against which to assess the impact of the intervention. However, this does not allow for any change in the condition of the patients that could have occurred spontaneously. Although MS can be a relapsing and remitting disease, it appears that in the majority of these cases, the disease was stable.

The sample size of the 11 longitudinal or case series studies ranged from 6 to 93, with many at the lower end of the range. Some of the studies may not have had adequate levels of statistical power and most did not attempt to justify their sample size.

Generally there was an absence of data analysis using statistics in the included studies, with many of the

studies resorting to qualitative analysis.

Effect on Spasticity (Table 8)

The studies showed an overall positive outcome for patients treated with intrathecal baclofen. All 15 studies reported positive findings. In studies that reported the Ashworth scale, scores fell almost universally by 2-3 points typically from 3-4 pre-implantation to 1 after treatment. Similarly, there was a near universal abolition of spasms, which was reflected in spasm frequency scores.

Table 8: Summary of studies included in the systematic review by Beard et al.(18)

Study	Design	Dose	Patients	Results
Saltuari et al. 1992 Austria	Prospective longitudinal uncontrolled	Mean final dose for MS patients 239 ug/day. Treatment duration 2-24 months	N=11, of whom 6 had MS Age 30-57years Disease duration 6-27 years	Results in MS patients not reported separately. Mean Ashworth score: For knee flexion reduced from 3.4 to 1.25 For knee extension from 3.4 to 1.4 Patellar reflex score reduced from ~3.9 to ~1.4 (reflex assessed on a 6 point scale). One MS patient reported to be able to use staircase. 4 catheter dislocations, one catheter break, one catheter torsion.
Becker et al. 1995 Canada	Prospective longitudinal uncontrolled	Mean dose at followup for MS patients 542 ug/day Treatment duration 13-34 months	N=9, of whom 6 had MS Age 34-56 years All were nonambulatory and many could not sit properly owing to their severe spasticity. The MS patients were all severely disabled with little or no leg function and marked arm weakness. 6/9 were unable to live at home. Average duration of MS 16.5 years.	Nursing Assessment: Major improvements in transfers (5/6), pain control (4/6), nursing care (5/6) and skin breakdown (5/6). Self-reported satisfaction survey of MS patients (1-5 score): All items showed major improvements in particular the ability to transfer, seating ability, personal hygiene, sleeping ability and pain control. Place of residence: 3/6 MS patients who were previously hospitalized were able to be discharged. # days in hospital: Average time spent in hospital reduced from 108 to 28 days per year. A number of complications including: surgical catheter revisions, pseudomeningocele repair and problems with pump refills.
Broggi et al. 1993 Italy	Prospective longitudinal uncontrolled	Mean dose in MS patients 178 ug/day. Mean duration of treatment 9 months	N=12, of whom 4 had MS. Mean age 50 years. Mean duration of disease 16 years. Unresponsive to oral therapy. Mean Ashworth score 3.8. All MS patients were bedridden.	Mean score before treatment was 3.8. This feel to 1.8 after treatment. Muscle spasms were abolished. No reported side effects in MS patients. There were pump related complications in other patients.
Penn et al. 1989 USA	**Double-blind Crossover RCT**	**100-150 ug/day or saline administered for 3 days in randomized**	N=20, of whom 10 had MS. Ages 31-62 years. One MS patient able to walk a short distance with crutches, the rest wheelchair bound.	In MS patients: No explicit results given for the short-term crossover trial, but period of baclofen infusion said to have been correctly identified by each assessment.

		crossover trial. Long term followup for mean of 19 months (mean dose 223 ug/day).	Mean Ashworth score 4.0.	In long-term followup, mean Ashworth score decreased from 4.01 to 1.05; mean spasm score decreased from 2.9 to 0.2. Of 20 patients, in 26 months followup, 2 catheters dislodged, one pump failure, one painful implant site.
Parke et al. 1989 USA	Long term followup	67-550 ug/day 3 and 6 months followup	N=8, of whom 4 had MS. May be same patients as included in other studies from the same centre.	Ashworth score reduced from 4 or 5 to 1 in all 4 MS patients. Bladder care score improved in all 4 patients (indwelling urinary catheter removed in 1 patient), dressing skills improved in 2 of 4 patients.
Penn (1992) USA	Case series	Mean initial dose 200 ug/day	N=66, of whom 33 had MS. Presumably some of the same patients as included in other studies from the same centre.	For all patients: Ashworth score: pre-implantation mean score ~3.7 falling to ~1.4 after implantation, maintained for up to 81 months. Spasm scale (0-4): pre-implantation mean score ~2.9 falling to 0.8 after implantation, maintained for up to 81 months. Complications: 1 meningitis, 1 pocket infection, 19 fungal infection of pumps (no clinical impact, all replaced), 9 pump failures out of 91 pumps, 25 catheter complications (various), 5 procedural complications. Complications of baclofen: drowsiness (n=22), dizziness (n=10), blurred vision (n=10), slurred speech (n=6).
Broseta et al., 1989 Spain	Prospective longitudinal uncontrolled	60-172 ug/day. Mean followup 5 months.	N=8, of whom 4 had MS. Age 27-54 years. All had severe spasticity and were unresponsive to oral treatments. Ashworth score 2-4. 4 cases were either in a wheelchair or bedbound.	All patients showed a reduction of at least one point on the Ashworth scale. All patients showed a reduction in frequency of spasms. All 4 cases had increased walking ability, transfers and daily activity. The nonambulatory patients gained only in QoL and comfort.
Coffey et al., 1993 USA	**Screening protocol was a double-blind RCT, followed by open label longitudinal study**	**Mean starting dose 171 ug/day. Mean dose at followup 320 ug/day. Placebo Patients followed up after a mean of 19 months (5-41 months).**	N=93 patients screened, of whom 31 had MS. 75 patients had a pump implanted, of whom 27 had MS. Average age 42 years. All had severe chronic spasticity and were refractory to oral drugs.	Ashworth score: mean score decreased from 2.9 to 1.6. Frequency of spasm score (0-5): mean score reduced from 2.7 to 0.7. One patient received an overdose due to human error. 3 mechanical failures, 6 wound complications, 22 catheter complications out of the 75 implantations.
Dressnandt et al., 1995	Prospective longitudinal	Mean of 61 months. At end of 1st year,	N=27, of whom 20 had MS. Ages 38-66 years.	Ashworth score: decreased in all 20 MS patients.

Germany	uncontrolled	mean dose was 189 ug/day.	Average age of MS patients was 52 years. All with severe paraspasticity or tetraspasticity.	Frequency of spasm score: decreased in all 20 MS patients. (N.B., the primary outcome reported in this trial was the ability to withdraw intrathecal baclofen after prolonged treatment. This was reported to be possible in 5 MS patients).
Gianino et al., 1998 USA	Prospective longitudinal uncontrolled	Mean dose at 12 months 298 ug/day.	N=25, of whom 15 had MS. All had intractable spasticity of spinal origin. Most were paraparetic, 6 were quadriparetic, 1 hemiparetic and 1 monoparetic. Mean age 39 years.	9 patients withdrew due to questionnaire fatigue. Ferrars and Powers QoL index: No change between baseline and 2 months. It was felt that this lack of change was due to the emphasis of the QoL on nonphysical aspects. SIP improved from 29.7 ot 21.7 (p=0.8) Physical subscore went from 38.5 to 31 (p=0.001). Psychological subscore went from 20.8 to 13 (p=0.025). Ashworth score: decrease from 3.8 to 1.5 (p value not stated). Frequency of spasm score: 2.6 to 0.5 (p=0.00001).
Lazorthes et al., 1990 France	Prospective longitudinal uncontrolled Mean followup was 18 months (range 4-43 months).	Individual doses in MS patients ranged from 100 250 ug/day.	N=18, of whom 6 had MS. MS patients ages 40-56 years. All patients had severe, debilitating spasticity and were unresponsive to oral treatment.	Ashworth scale: 2-4 point improvement on all 6 patients. Modified Davis and Gray scale for evaluation of motor performance: 1/6 large improvement, 1/6 moderate improvement, 4/6 no improvement in function. Abolition of painful spasms in 5/6. Functional improvement was noted in 1 MS patient. Functional improvement was greater in patients with traumatic lesions as opposed to those with MS. 2 MS patients had serious complications (overdose, meningitis).
Middel et al., 1997 Netherlands Cost analysis of this study is covered in the paper by Postma et al.	**Double-blind RCT for 13 weeks followed by longitudinal observational study for 52 weeks.**	**75-150 ug/day. Placebo**	N=22, of whom 12 had MS. Aged 19-70 years. Baclofen N=12 Placebo N=10 All 22 received intrathecal baclofen in the observational study. All patients had chronic disabling spasticity and were not responding to oral medication.	Fall in Ashworth, spasm and pain scores in treated compared to placebo groups at 3 months. Effect sizes 0.2, 1.4 and 0.94, p<0.05, <0.01, <0.05, respectively. No significant differences in the change in SIP or HSCL scores. Significant fall in Ashworth, spasm and pain score on treatment at 3 (not for pain) and 12 months. Significant improvement in SIP, HSCL on treatment at 3 and

				12 months.
Ochs and Tonn, 1996 Germany	Prospective longitudinal uncontrolled	Mean dose 199 ug/day at 1 year. Study duration up to 5 years.	N=70, of whom 59 had MS. Ages 35-69 years. All patients suffered from spinal lesions resulting in severe spasticity. Mean Ashworth score 4.1.	2 MS patients died during the study but this was thought to be unrelated to their treatment. Reduction in muscle tone at on average 2 points below the initial baseline Ashworth score. This was sustained over 5 years in 12 patients. "Spontaneous spasms reduced but less reliably than muscle tone." At baseline, 54% (38/70) were bedridden. After 6 months 22 of the 38 could leave bed and use a wheelchair. Initially, 14 patients were wheelchair bound. After treatment 4 of these were able to stand. Subjective assessment: after 6 months 19/22 patients and 20/22 physicians rated the outcome as good or excellent.
Patterson et al., 1994 UK	Prospective longitudinal uncontrolled	Initial mean dose 223 ug/day. Effective mean dose 485 ug/day. Treatment duration varied from 9 to 79 months.	N=21, of whom 15 had MS. Mean age 46 years (range 24-67) All patients had severe spasticity and were unresponsive to oral treatment. None was ambulant.	7 patients died but this was thought o be unrelated to the treatment. Complications in 9 patients led to the pump being removed. This included infections leading to meningitis in 5 patients. Ashworth scale: Complete and sustained fall in score in 16/21 patients. In 4 other patients there was short term benefit. Frequency of spasm score: 18/21 patients showed a complete absence of spasms. 15/15 MS patients showed a complete absence of spasms. Barthel index: no change in any patients, possibly due to inappropriateness of this measure. 16/21 patients showed sustained improvements but the 2 patients who showed the greatest improvements in terms of mobility and ability to drive did not have MS.
Penn and Kroin, 1985 USA	Prospective longitudinal uncontrolled	Initially 12-200 later 12-400 ug/day for 7 months.	N=6, 3 with MS. All had severe rigidity in lower limbs (Ashworth score 4-5) and 5/6 had frequent spasms. 5/6 non mobile 1/6 partially mobile. Average age of 36 years (range 19-54 years)	1 patient withdrew. All patients showed an immediate and long lasting return from an Ashworth score of 4-5 to 1 (normal tone). Spasms were controlled in all patients and stretch reflexes were reduced in half. None of the patients had any of the central side effects which they had with oral baclofen. Functional improvement in ADL (?) reported.

Table reproduced with permission from the NCCHTA; From Beard S, Hunn A, Wight J. Treatments for spasticity and pain in multiple sclerosis: a systematic review. [Review] [154 refs]. Health Technology Assessment (Winchester, England) 2003; 7(40):iii, ix.

Regarding the use of intrathecal baclofen pumps to control spasticity in MS patients, Beard et al. (18) made the following conclusions:

- The studies indicate that patients with severe spasticity are likely to benefit from treatment with intrathecal baclofen in terms of a reduction in spasticity, improved ability to sit in a wheelchair, possibly of standing and improved nursing care.

- Patients with less severe disability may also benefit from improvements in care, with ability to transfer and the likelihood of a considerable reduction in painful spasms .

- There is some evidence that bedridden patients with very severe forms of MS are unlikely to benefit in terms of improved functionality or mobility but may benefit from generally improved care and hygiene.

- In spite of the weaknesses of the study designs, one can conclude from the benefits seen in these studies that intrathecal baclofen has a positive outcome for MS patients with severe spasticity.

Institute for Clinical Systems Improvement (ICSI), United States, September 2000

ICSI conducted a review of intrathecal baclofen for lower extremity spasticity associated with cerebral palsy.

Intrathecal baclofen is typically considered for 2 particular groups of patients:

1. Patients with either spastic diplegia or spastic quadriplegia who are ambulatory (with or without assistive devices) but who have inadequate leg strength and who use their spasticity to stand and walk. The goal of treatment is to walk with less effort.
2. Nonambulatory patients with severe spasticity (upper and lower extremities). The goal of treatment is to facilitate the care of these patients.

ICSI summarized the following studies examining the effects of intrathecal baclofen in patients with cerebral palsy (Table 9).

Table 9: Studies examining intrathecal baclofen in children with cerebral palsy From ICSI.

Study	Design	Dose	Patients	Results
Dralle et al., 1989	Case series	Continuous daily dose of 25-700 ug required. Dose increases required over time.	N=10 Ages 3-10 years	Reduced spasticity.
Albright et al., 1991	Double-blind RCT Placebo	25, 50, or 100 ug of baclofen or placebo on successive days.	N=17 Mean age 12.2 years	Muscle tone assessed at 2, 4, 6, and 8 hours after injection; upper extremity function at 4 hours. Mean muscle tone in lower extremity decreased within 2 hours of treatment and remained low for next 6 hours (p=0.0001). No change in muscle tone of the upper extremity. 3 dose levels produced a similar response in lower extremity muscle tone; each dose significantly different from placebo (p<0.05). No neurological side effects with 25 ug dose. With 50ug, 2 patients experienced lethargy, agitations and disorientation that resolved without incident.
Albright et al., 1993	Observational	?	N=37, of whom 33 spasticity related o cerebral palsy. Group 1 = moderately severe spastic quadriparesis (n=25) and capable of self-care. 22 patients were ambulatory. Group 2 = severe spastic quadriparesis (n=12) and were incapable of self-care and spasticity impeded care.	Muscle tone assessed at baseline and at 3, 6, 12, 24, and 36 months (for 37, 32, 30, 22, 13 and 6 patients respectively. Upper extremity function and activities of daily living assessed at baseline and at 6 months. Overall: Mean lower extremity muscle tone decreased at 3, 6, 12 and 24 months (p=0.001) with too few data at 36 months. Mean upper extremity tone decreased at 6, 12, and 24 months (p=0.008). Muscle tone related to baclofen dose for both the upper (p=0.02) and lower (p=0.001) extremities. Group 1: Lower extremity, but not upper extremity muscle tone decreased (p=0.007). Upper extremity timed tasks performed faster (p=0.04. Activities of daily living improved (p=0.04).

				Group 2: Upper and lower extremity tone decreased (p=0.001). No changes in activities if daily living. Adverse Effects: No adverse cerebral effects noted. Temporary side effects observed in 5 patients. 5 patients required operation to correct catheter-related problems. 8 pumps removed including 4 due to infection, 2 due to recurrent CSF leaks, and 2 due to inadequate therapeutic benefit.
Gerszten et al., 1998	Case series. Effect of IT baclofen on the need for orthopedic surgery.	?	N=48, all with spastic CP. Age range 5-43 years. Followed for 2 years.	At least 1 orthopedic procedure completed in 29 (60%) of patients before pump implanted. At pump placement time, surgery planned in 28 (58%) patients. Surgery performed in 10/28 patients; remaining 18 patients judged to no longer require surgery. Pump malfunction observed in 11 (23%) of patients.
Wiens, 1998	Case Series Retrospective	Oral baclofen was not effective for these patients.	N=17 Age range 5-17 years.	Lower extremity spasticity decreased (p<0.001)at both 1 and 3 months. Upper extremity spasticity unchanged. Improved mobility noted for 71% Improved ability to perform activities of daily living associated with hygiene was noted for 35% Improved feeding for 29%. Complications included CNS changes in 29%, pump malfunction in 6%, catheter malfunction in 12% and CSF leaks in 29%.
Van Schaeybroeck et al., 2000	Case series.	11 patients tested for IT baclofen response. 8/11 had positive response, but 2 did not have sufficient followup data (for 2 years).	N=6, 5 with CP Age range 15-44 years old. Followup data for 2 years.	Dose dependent response (Ashworth scale) seen following bolus doses of 25, 50, 75, and 100ug; significantly different from placebo (p<0.0001), although there was a significant reduction in spasticity following placebo (p<0.009). During first 12 months, spasticity scores lower than at baseline (p<0.001). Pain decreased and QoL reported to be improved by all patients. Overall function scores unchanged. 5/6 patients discontinued oral antispasmodic drugs.

				1 mechanical complication (disconnected catheter).
Gilmartin et al., 2000	Multicentre 12 site study. Phase 1 screening RCT of 50ug baclofen bolus versus placebo bolus. Spasticity assessed at 0.5, 1, 2, 4, 6, and 24 hours after treatment. If spasticity decreased and patient did not respond to the placebo injection, patient eligible for pump implantation. If not, 75 ug and 100 ug doses attempted. Phase 2. Open label, long term, continuous infusion study. Spasticity assessed at 2 weeks, monthly for 6 months and then at 3 month intervals.	Bolus 50ug, 75 ug or 100 ug.	N=51 in Phase 1. Ages 4-31.3 years, mean 10.3 years.	<u>7 withdrew after Phase 1:</u> 3 placebo responses 2 no responses to 50 ug dose 1 meningitis 1 adverse effect of treatment. <u>Pumps implanted in 44 patients.</u> 7 withdrew from Phase 2: 2 infection in pump pocket 2 family issues 1 to become pregnant 2 deaths unrelated to baclofen treatment. 38 patients (74.5%) responded positively to the 50 ug bolus dose. Of those, there was improvement in average Ashworth score for lower extremities at 2, 4, 6, 8 hours ($p<0.001$). This response was different from placebo ($p<0.001$). Upper extremity spasticity reduced ($p<0.001$). The remainder of the 44 patients responded to a 75ug or 100ug bolus. Among the 44 patients who received a pump, lower extremity spasticity was decreased from baseline at 6 months (n=42), 12 months (n=40) and 39 months (n=7). Mean dose at start was 75 ug; at 39 months mean dose was 402.5 ug/day. Adverse events reported in 42 of the initial 51 patients (total of 205 adverse events). Most events were minor. Following events occurred in $\geq$2% of the population: Hypotonia (15.1%) Seizure (9.3%) Somnolence (8.8%) Headache (6.8%) Vomiting (6.8%) Nausea/vomiting (4.4%) Nausea (3.0%) Device-related adverse effects included 39 procedure-related events (7 pocket seroma, 5 pocket infection, 4 catheter dislodged, 3 CSF leak, 20 other) and 20 system

				related events (2 catheter break, 2 catheter dislodged, 2 back pain at catheter site, 14 other).
Gerszten et al., 1997	Case series	?	N=24, of whom 21 had spastic CP and 3 with spasticity secondary to spinal cord injury. Age range 9-30 years.	Ambulation rated by physicians and therapists as improved in 9 patients, unchanged in 12 and worse in 3 patients. Patients and family members rated 20 as improved, 3 as unchanged and 1 as worse. 3 patients had complications: 1 pump infection, 1 catheter disconnection (proximal revision of catheter) and 1 catheter complication (required 2 separate revisions).

From: Institute for Clinical Systems Improvement (ICSI). Dorsal rhizotomy and intrathecal baclofen for lower extremity spasticity associated with cerebral palsy. Bloomington, MN: ICSI; 2000

ISCI concluded:

- Intrathecal baclofen has the advantage of utilizing a trial dose to determine if the baclofen is effective and allowing the adjustment of the treatment dose, if needed.
- Studies of intrathecal baclofen have focused on spasticity and range of motion measures. There are limited data on functional outcome measures and a lack of long-term followup.

Trent Institute for Health Services Research (UK), January 2000

The purpose of the review by Sampson et al. (3)was to identify and review the evidence base for the use of intrathecal baclofen in the treatment of spasticity and to outline the potential cost implications of providing the treatment for all patients who may benefit.

Inclusion criteria consisted of: Trials investigating patients with CP, MS, SCI, traumatic brain injury or hypoxic brain injury; trials including more than 1 patient; average followup period of at least 6 months.

Outcomes of interest were: Function; quality of life; pain; subjective patient/caregiver report of effectiveness; or health service use.

Type of Evidence Available
Ninety-four studies were identified of which 68 were excluded. Twenty-six original studies and 1 meta-analysis met the criteria for inclusion in the review of effectiveness.

Studies were sorted according to origin of spasticity:
- Eight studies included patients with spasticity of spinal origin
- Six studies included patients with spasticity of cerebral origin
- Twelve studies either included patients with spasticity of cerebral origin and patients with spasticity of spinal origin, or, it was not clear whether the origin of spasticity was spinal or cerebral in some patients.

Quality of Evidence
Sampson et al. stated that most studies were before and after observational trials. One study was a RCT for part of the trial; the randomized part lasted 13 weeks.

Many trials did not describe the methods that were used to measure the functional outcomes. For example, some trials stated that post-treatment some patients were easier to care for but gave no indication of how this had been assessed.

Some trials used validated outcome measures, but other trials used outcomes measures that had not necessarily been demonstrated as being reliable and valid.

Many reports did not provide a statistical analysis.

Sampson et al. stated that although the Ashworth and spasm scores provide a useful way of monitoring spasticity, these scores do not provide information about how spasticity affects patients' QoL. In view of this and the fact that the meta-analysis by Creedon et al. already summarized the data on Ashworth and spasm cores, the subsequent descriptions of trials included in this review do not include further descriptions of the effect of intrathecal baclofen on these measures.

Effects of Intrathecal Baclofen Infusion in Patients with Spasticity of Spinal Origin

- Eight studies that included only patients with spasticity known to be of spinal origin fulfilled the inclusion criteria (N=160 patients, including 78 SCI and 65 MS).
- The meta-analysis suggested that intrathecal baclofen may be effective in reducing spasticity of spinal origin in at least 92% of patients.
- In terms of quality of life and functional outcomes, the only RCT demonstrated no significant difference between placebo and baclofen groups in quality of life/functional measures at 3 months post-implantation.
  - The largest case series of intrathecal baclofen in spinal spasticity used subjective outcome measures and did not report the numbers of improved patients (Ordia et al. 1996).
  - According to Sampson et al., the remainder of the studies were uncontrolled open followup studies, mainly using subjective outcome measures and usually involving relatively small numbers of patients.(3)

Effects of Intrathecal Baclofen Infusion in Patients with Spasticity of Cerebral Origin

- Six studies which included only patients with spasticity of cerebral origin fulfilled the inclusion criteria (N=111 patients, including 63 with CP; the majority of the remaining patients had traumatic or hypoxic brain injury).
- The meta-analysis suggested that intrathecal baclofen may be less effective in reducing spasticity in patients with spasticity of cerebral origin than in patients with spasticity of spinal origin.
- In terms of quality of life and functional outcomes, Sampson et al. stated that the studies were based on uncontrolled open followup studies mainly using subjective outcome measures and usually having relatively small numbers of patients.

Effects of Intrathecal Baclofen on Different Outcome Measures

- Different outcome measures were used in different studies and were often subjective.
- Many studies did not provide denominator data (e.g., report that 2 patients had decreased pain, but not say how many patients suffered from pain before treatment).
- Sampson et al. (3)summarized the outcomes related to mobility, activities of daily living, dependency and the need for nursing care and other quality of life issues. Only studies where appropriate denominator data were provided were included. The following terms were used in Tables 5-9 below:

Mixed adults	Study included patients with spasticity of both cerebral and spinal origin.
Cerebral	Study only included patients with spasticity of cerebral origin
Spinal mainly adults	Study only included patients with spasticity of spinal origin, most of whom were adults.

Table 10 shows that overall:

- 50/76 (66%) of bedridden patients became able to sit in a wheelchair
- 31/36 (86%) had improved ability to sit comfortably
- 13/18 (72%) improved wheelchair mobility
- 25/26 (96%) had improved ability to transfer
- 4/36 (11%) of wheelchair bound patients became ambulatory (with aids)
- 15/47 (32%) ambulatory patients improved their ability to walk and 4/47 (9%) had deterioration of their ability to walk
- 3/29 (10%) became able to drive

Table 10: Outcomes related to mobility From Sampson et al.(3)

Outcome	Studies	Patient Condition	Result
Bedridden patients becoming able to sit in wheelchair	Becker	CP or ABI adults	8/12
	Stewart-Wynne	Mixed adults	6/6
	Ochs	Mixed adults	22/38
	Zierski	Mixed adults	14/20
			Overall 50/76 (66%) bedridden patients became able to sit in a chair
Improved ability to sit comfortably	Becker	6 MS patients	ON a 0-5 scale, average 3 point improvement in ability to sit
	Mertens	Spinal adults	15/15 improved ability to sit comfortably
	Patterson	Mixed adults	16/21 improved ability to sit comfortably
			Overall 31/36 (86%) had improved ability to sit comfortably
Improved wheelchair mobility	Becker	CP or ABI adults	3/6
	Zierski	Mixed adults	10/12
			Overall 13/18 (72%) improved wheelchair mobility
Ability to transfer improved	Becker	Mixed adults	8/9 major improvement
	Azouvi	12 adults with thoracic/lower cervical lesions	Average improvement from 3.5 to 6. on a 1-7 scale
	Mertens	Spinal adults	17/17 improved ability to transfer
			Overall 25/26 (96%) had improved ability to transfer
Wheelchair bound patients becoming ambulatory (with aids)	Concalves	CP or ABI adults	¼ wheelchair bound developed "handicapped walking"
	Ochs	Mixed adults	1/27
	Penn	Mixed adults	2/5
			Overall 4/36 (11%) had developed "handicapped walking"
Ambulatory patients improving their capacity to ambulate	Broseta	Mixed adults	1/7
	Azouvi	Adults with lower cervical/thoracic lesions	5/12 (including 2/12 who became able to climb stairs)
	Zierski	Mixed adults	3/5
	Penn	Mixed adults	1 of 2 ambulatory patients lost ability to walk
	Gerszten	CP or ABI mean age 18	6/21 improved walking ability including 4/7 who only walked in therapy became able to walk at home. 2/6 who only walked at home

			became able to walk in the community (note 3 patients also had deterioration in walking ability).
			Overall 15/47 (32%) ambulatory patients improved their ability to walk and 4/47 (9%) had deterioration of their ability to walk.
Patients becoming able to drive	Parke	Mixed adults	1/8
	Patterson	Mixed adults	2/21
			Overall 3/29 (10%) became able to drive.

Table reprinted with permission; From Sampson FC, Hayward A, Evans G, Touch S, Morton R, Vloeburghs M et al. The effectiveness of intrathecal baclofen in the management of patients with severe spasticity. 2000. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield. Guidance Note for Purchasers: 00/01

Table 11 shows that overall 45/62 (73%) of patients had some improvement in Activities of Daily Living (ADL) scores; these improvements were usually not observed in bedbound patients.

Table 11: Subjective assessments of activities of daily living (ADL) From Sampson et al.(3)

Outcome	Studies	Patient Condition	Result
Activities of daily living improved (subjective impression – no scoring systems used)	Albright	CP or ABI mainly children	19/25 self-caring patients 0/7 non self-caring patients
	Gerszten	CP or ABI mainly children	20/24 (deteriorated in 2/24)
	Stewart-Wynne	Mixed adults	6/6
			Overall 45/62 (73%) showed some improvement in ADLscores. Improvements in ADL scores were usually not seen in bedbound patients.

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Table 12 shows that overall:

- 83/90 (92%) patients had improved ease of nursing care
- 19/23 (83%) of patients had improvements with skin integrity problems

Table 12: Outcomes related to dependency levels and nursing From Sampson et al.(3)

Outcome	Studies	Patient Condition	Result
Place of residence	Becker	Mixed adults	Of the 3 patients who were hospitalized prior to intrathecal baclofen, 2 became able to live in the community and 1 in a group home. Of 3 patients in chronic care institutions prior to intrathecal baclofen, 2 were able to move to a group home and one moved to hospital (due to comorbidities and progression of

			MS).
Need for personal attendant services	Nance	Mixed adults	2/7 had decreased need for personal attendants.
Ability to dress	Ochs	Mixed adults	8/12 patients who required major help in dressing required only a little help in dressing 6 months after intrathecal baclofen. 1/4 patients who required a little help became able to dress without help.
Eating alone	Ochs	Mixed adults	2/9 who required help became able to eat alone.
	Parke	Mixed adults	5/7 who required help became able to eat alone.
Dependency level	Stewart-Wynne	Mixed adults	6 adults – no measurable change in dependency levels.
Improved ease of nursing care	Albright	CP or ABI mainly children	6/7 nonself-caring patients
	Becker	CP or ABI adults	18/18
	Becker	Mixed adults	8/9
	Patterson	Mixed adults	16/21
	Lazorthes	Mixed mainly adults	18/18
	Mertens	Spinal adults	17/17
			Overall 83/90 (92%) had improved ease of nursing care.
Skin integrity	Becker	Cerebral adults	Of 11 chronic decubital ulcers, 5 healed and 5 improved.
	Becker	Mixed adults	6/9 improved skin condition.
	Parke	Mixed adults	3/3 with skin problems had resolution of problems.
			Overall 19/23 (83%) of patients with skin integrity problems showed improvements.

Table reprinted with permission; From Sampson FC, Hayward A, Evans G, Touch S, Morton R, Vloeburghs M et al. The effectiveness of intrathecal baclofen in the management of patients with severe spasticity. 2000. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield. Guidance Note for Purchasers: 00/01

Table 13 shows that overall:

- 59/66 (89%) patients with spasm related pain had relief or complete resolution
- 27/33 (82%) had improved urinary function

Table 13: Outcomes related to quality of life (QoL) From Sampson et al.(3)

Outcome	Studies	Patient Condition	Result
Pain	Broseta	Mixed adults	9/10 with pain became pain free
	Lazorthes	Mixed	14/16 resolution of painful spasms
	Loubser	Spinal injury adults	6/6 with musculoskeletal pain had complete resolution.
	Mertens	Spinal adults	9/9 with spasm related pain became pain free
	Sahuquillo	Mixed adults	8/8 with spasm related pain had relief.
	Zierski	Mixed	13/17 with spasm related pain became pain free.
			Overall 59/66(89%) of patients with spasm related pain had relief or complete resolution.
Sleeping	Becker	Mixed adults	On a 0-5 scale, sleep improved an average of 2.9 points, from 1.6 to 4.5
	Penn	Mixed adults	7/7 had improved sleep.

Sexual functioning	Ordia	Spinal adults	4/59 resumed sexual activity (all females)
	Loubser	Spinal injury adults	1/7 improved sexual functioning
Social	Patterson	Mixed adults	2/21 improved social life
	Penn	Mixed adults	3/7 returned to work
	Middel		At 1 year, no change, no psychosocial dimensions of Sickness Impact Profile (SIP) score
	Ordia	Spinal adults	2/59 became employed.
	Loubser	Spinal injury adults	3/7 became able to take vacations
Urinary function	Broseta	Mixed adults	5/9 bladder function improved.
	Parke	Mixed adults	2/4 who were dependent became independent
	Penn	Mixed adults	4/4 who were incontinent between catheters became continent between catheters.
	Nanninga	Spinal adults	4/4 who were incontinent between catheters became continent between catheters. 3/3 patients with indwelling catheters became able to self catheterize.
	Concalves	CP or ABI adults	2/2 with bladder dysfunction showed improvement.
	Sahuquillo	Mixed adults	Of 3 with indwelling catheters, 2 had minimization of leaks and 1 became able to self catheterize. 4/4 with voluntary voiding had decreased nocturia.
			Overall 27/33 (82%) had improved urinary function.

Table reprinted with permission; From Sampson FC, Hayward A, Evans G, Touch S, Morton R, Vloeburghs M et al. The effectiveness of intrathecal baclofen in the management of patients with severe spasticity. 2000. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield. Guidance Note for Purchasers: 00/01

Table 14 shows that overall, functional outcome results were variable between studies.

Table 14: Studies using a validated scoring system From Sampson et al.(3)

Studies	Patient Condition	Result
Azouvi	Spinal adults	Functional Improvement Measure. 7-point scale. Overall improvement in motor but not cognitive domains. Minimum 2 point improvement in bathing, dressing lower body, transfers and locomotion.
Gianino	Spinal adults	Ferrans and powers QoL index – no improvements Sickness Impact Profile (SIP) (0-100 scale) improved from 29.7 to 21.7. Physical subscore improved from 38.5 to 31.0. Psychological subscore improved from 20.8 to 13.0. Changes were measured at 12 months in 16 patients and were statistically significant ($p<0.005$).
Mertens	Spinal adults	Functional Disability Score – composite score measuring pain, spasms, wheelchair use, transfers and washing/dressing each on a 4-point scale decreased from 13.4 to 5.8 ($p<0.0001$) (n=17 patients).
Middel	Spinal adults	Hopkins Symptom Checklist and SIP – no difference between placebo and intervention group at 3 months. At 12 months physical subscore of SIP improved from 41.5 to 31.5. No change on psychosocial subscore.
Patterson	Mixed adults	0/21 showed improvements in Barthel score.

Table reprinted with permission; From Sampson FC, Hayward A, Evans G, Touch S, Morton R, Vloeburghs M et al. The effectiveness of intrathecal baclofen in the management of patients with severe spasticity. 2000. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield. Guidance Note for Purchasers: 00/01

Complications of Intrathecal Baclofen reported in the meta-analysis by Creedon et al.(13)

The studies that were included in the meta-analysis by Creedon et al.(13) also examined complications. Studies that reported side effects, and in which the type of pump used was known, were summarized (Table 15). Overall, the majority of complications associated with intrathecal baclofen infusion consisted of local infections, catheter problems requiring surgery and pump removal due to complication.

Table 15: Complications associated with intrathecal baclofen infusion From Sampson et al.(3)

Complication	Pump (n=222)
Overdose	5 (2%)
Pump removal due to complication	16 (7%)
Catheter problems requiring surgery	37 (17%)
Local infection	9 (4%)

Table reprinted with permission; From Sampson FC, Hayward A, Evans G, Touch S, Morton R, Vloeburghs M et al. The effectiveness of intrathecal baclofen in the management of patients with severe spasticity. 2000. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield. Guidance Note for Purchasers: 00/01

A summary of the effectiveness of intrathecal baclofen infusion by Sampson et al.(3) is as follows:

- Continuous intrathecal baclofen infusion produces a reduction in severe spasticity of spinal origin in most patients. The effect on spasticity in patients with severe spasticity of cerebral origin is likely to be less, but beneficial change was also seen in this group.
- The QoL evidence is generally poor (consisting almost entirely of small, open, uncontrolled followup studies with subjective outcome measures and a failure to report results separately in different patient groups). However, the quantity of the evidence is large and many studies show effects in some patients.
- Decisions about whether or not to use intrathecal baclofen infusion need to be based on an understanding of the likely benefits in patients with different levels of function:
    - Patients with very severe spasticity who are bedbound and difficult to nurse are likely to benefit from being able to sit out of bed. Nursing care is also likely to be easier. Such patients are unlikely to have improvements in ADL.
    - Patients who use wheelchairs but have great difficulty in being seated in the chair are likely to benefit by being able to sit much more comfortably.
    - Patients with a reasonable degree of remaining function may show some improvements in their ability to perform important functions such as transfers, feeding, dressing or wheelchair mobility. Most studies do not quantify the level of improvement so it is difficult to judge from the literature how great that improvement may be. Failure to show large improvements in functional measures such as the Sickness Impact Profile (SIP)suggest that such improvements may be modest. It is unlikely that patients will show dramatic improvements in function, although there are a few reports where this has occurred. The vast majority of patients will still require help to perform many of their activities. However, in severe disability even modest improvements in function may be very important to patients.
- The evidence for using intrathecal baclofen infusion to improve walking ability is very limited. Up to one-third of ambulatory patients may show some improvements in ambulation. Some patients may find that the loss of tone makes walking more difficult.
- Significant pain related to spasms and problems with skin integrity strengthen the case for using intrathecal baclofen infusion. In addition, this technology may also improve urinary function, but

patients may still need to self-catheterize.

Cochrane Review: Pharmacological Interventions for Spasticity Following SCI, 2003

The objective of the review by Taricco et al. (16) was to assess the effectiveness and safety of baclofen and other drugs for the treatment of long-term spasticity in SCI patients as well as the effectiveness and safety of different routes of administration of baclofen .

Databases searched included the Injuries Group Specialized register, the Cochrane Controlled Trials Register, Medline, Embase and CINAHL up to 1998. Selection criteria consisted of all parallel and crossover RCTs including spinal cord injury patients complaining of "severe spasticity". Studies where less than 50% of patients had a spinal cord injury were excluded.

Overall, 9 trials out of the 53 retrieved met the inclusion criteria. Fourteen studies are still being assessed by the authors. Of the 9 studies, 2 focused on intrathecal baclofen.

These included a 1989 study by Penn et al. (20) that was previously reported in the assessment by Beard et al. (18) and a 1992 study by Kravitz (22) that is a substudy of the Penn et al. study. Six patients with an active pump already implanted were studied in order to evaluate the effect of baclofen infusion on electromyographic activity.

Taricco et al.(16) concluded that:

- Overall, there is insufficient evidence to assist clinicians in a rational approach to antispasticity treatment for SCI. Further research is urgently needed to improve the scientific basis of patient care.
- *The current rationale that assumes that a "decision tree approach" exists calling for the use of progressively more complex treatments whose sequence is guided by documented failures of previous steps appears particularly weak. This is why nonresponders eventually become candidates for intrathecal baclofen after previous failures with less invasive steps.*

(16) et al. stated the following implications for research:

- This review clearly indicates that further research is urgently needed to assure that patients with SCI receive evidence-based care.
- Further studies should include larger groups of patients and most importantly, use more clinically relevant measures of treatment effects, including Activities of Daily Living (ADL) and QoL measures administered at appropriate time intervals with respect to the realistic goals of patient recovery.
- The vast majority of currently available studies have too short a followup period to be able to realistically assess clinically relevant end points dealing with functional recovery.
- More head-to-head comparison studies are required to get a full picture of the cost-benefits profile of the interventions, especially if a "step by step" treatment strategy (from simpler to more complex protocols according to individual's clinical responses) has to be used.

Centre for Clinical Effectiveness (Australia) (March 2000)

Villanueva and Anderson .(23) reviewed the evidence for the use of intrathecal baclofen for hereditary spastic paraplegia. A literature search was conducted (up to February 29, 2000). Overall, the authors found one systematic review published in 1997 (Creedon et al.(13)) and no studies on this topic published since 1997.

The systematic review by Creedon et al. examined the effectiveness of intrathecal baclofen on general severe spasticity. Data from 27 studies (490 patients) was examined. The study designs were varied: double blind placebo controlled RCTs (n=7); prospective open trials (n=17); combined designs (n=2); retrospective case series (n=1). The average age of patients was 36-years. The primary endpoints were changes in Ashworth and Penn scores, duration of followup and dose at last followup.

The following results from Creedon et al.(13) were reported:

- Mean Ashworth scores decreased form 3.9 to 1.6 ($p<0.001$)
- Mean Penn scores decreased from 3.5 to 0.7 ($p<0.001$)
- Cumulative success of 78.21% was reported
- Over 16 months, dose increased by an average of 250% from baseline

Summary of Health Technology Assessments of Intrathecal Baclofen

- Overall, HTAs suggest that intrathecal baclofen is an effective treatment for spasticity (Level 2 and Level 3 evidence).
    - This is supported by the 1997 meta-analysis by Creedon et al. .(13) who found statistically significant changes in both the Ashworth score and the spasm score before and after treatment in all patients, but particularly in patients with MS and SCI. The results for patients with CP were not statistically significant but did show a trend towards improvement. This may have been due to the low numbers of patients with CP included in the meta-analysis.
    - The meta-analysis (18)also showed that 92% of patients who had a pump installed were still using the pump at 1 year of followup, which may indicate that the problems experienced with the pump and catheter may be minor.
    - The Trent Institute for Health Services Research (3) conducted a review of the effectiveness of intrathecal baclofen in the management of patients with severe spasticity, and building on the Creedon review went on to look at functional outcome measures (with limitations). They found that intrathecal baclofen led to functional improvements including improvements in the ability to sit up in bed or to sit more comfortably in a wheelchair, improved nursing care and moderate improvements in activities of daily living.
    - The NHS R&D systematic review of treatments for spasticity in MS (last updated in 2000) by Beard et al.(18) reported on 15 trials (including 3 double blind trials that compared intrathecal baclofen to placebo) (Table 15). All 15 studies showed an overall positive outcome for patients treated with intrathecal baclofen. In studies that reported the Ashworth scale, scores fell almost universally by 2-3 points, typically from 3-4 pre-implantation to 1 upon treatment. Similarly, there was a near universal abolition of spasms, which was reflected in spasm frequency scores.
    - The NHS R&D review by Beard et al.(18) stated that there is a great need for more research into the treatment for spasticity in MS, including the development of better outcome measures which relate to functional ability and patients' QoL.

Summary of Medical Advisory Secretariat Review of Intrathecal Baclofen for Spasticity

A literature search performed after the most recent health technology assessment (ASERNIP-S) identified 8 studies that met the inclusion criteria. These studies are discussed below (Table 16).

Table 16: Quality of evidence

Study Design	Level of Evidence	No. Eligible Studies
Large RCT,* systematic reviews of RCT	1	
Large RCT unpublished but reported to an international scientific meeting	1(g) †	
Small RCT	2	
Small RCT unpublished but reported to an international scientific meeting	2(g)	
Non-RCT with contemporaneous controls	3a	3
Non-RCT with historical controls	3b	
Non-RCT presented at international conference	3(g)	
Surveillance (database or register)	4a	
Case series (multisite)	4b	
Case series (single site)	4c	
Retrospective review, modeling	4d	4
Case series presented at international conference	4(g)	

*RCT refers to randomized controlled trial
†g=grey literature

■ Zahavi et al. (24) evaluated the change in impairment, disability and health related functional status after 5 years in patients (N=21) with severe spasticity associated with multiple sclerosis or spinal cord injury, who received intrathecal baclofen (Level 3 Evidence). This study was a followup of a previous study by Middel et al. (19)

Inclusion criteria consisted of:
Patients ≥18 years of age with chronic disabling spasticity of spinal origin inhibiting personal care, sitting, lying and transfers, accompanied by pain and stiffness or disturbed sleep
Insufficient response to treatment with maximal doses of oral baclofen, dantrolene and tizanidine
Sufficient understanding of the consequences of treatment.

Exclusion criteria consisted of:
Pregnancy
Neurological symptoms of supraspinal origin
Allergy to baclofen

During a 4-year period (1991-1995), a programmable pump for injecting intrathecal baclofen was implanted in 38 patients. Since more patients in the first study were followed up for 26 weeks than for 1 year, the authors decided "to compare current measurements with those taken at the start of the study and at 26 weeks of followup as there were likely to be more data available."(24)

Of the 38 patients originally included in the study, 21 were available for followup. Seventeen patients were not included for the following reasons:

n=1 Pump removed due to an infection
n=3 Administration of intrathecal baclofen was discontinued for "various reasons"
n=9 Died from complications of the underlying spinal disease or other medical illnesses not related to the spinal disorder

n=2 Refused to participate in the study
n=2 Lost to followup

The mean age (standard deviation) of the patients was 54.6 (12.5) years and 53% (11/21) had progressive disease (MS in all cases). Among patients with non-progressive disease, 6 had spinal cord injury, 1 had adrenalopathy, 1 had anterior spinal syndrome, 1 had radiation myelopathy, and 1 had spinal angioma. The mean duration of treatment was 84.9 months.

Zahavi et al. summarized the results of the assessments of impairment (Ashworth scale and spasm score), disability (EDSS, AL and ISS) and health outcome measures (SIP and HSCL) at baseline, 26 weeks after baseline, and at the final evaluation.

For the final evaluation versus baseline values, there was significant improvement in the level of impairment (Ashworth scale and spasm score, $p<0.05$) and a significant worsening in the level of disability (EDSS, AI and ISS, $p<0.05$).

For the final evaluation versus 26 weeks after treatment values, there was a significant worsening in the level of disability (EDSS and ISS, $p<0.05$) and in one dimension (psychosocial) of perceived health status (SIP, $p<0.05$).

For the final evaluation versus baseline values, there is a discrepancy between significant improvement in the level of impairment using the Ashworth and spasm scores and the significant worsening in the level of disability. Similarly, for the final evaluation versus 26 weeks after treatment values, it is unclear as to why there was a significant worsening in the level of disability and in the psychosocial dimension of the perceived health status. The authors suggested that the following points may have played a role in these discrepancies:

- Several patients, particularly those with MS had cerebral symptoms such as cognitive dysfunction at followup. Cognitive abilities were also reduced in the elderly patients, who comprised a significant proportion of the study group. Help from family members and caretakers was needed and this may have influenced some results.
- The progressive nature of the disease may have affected the results of the perceived health status. More than half of the patients were >50 years old which may explain why no change was observed in the physical aspects of perceived health status. The psychosocial dimensions are not only related to achieving adequate control of spasticity and spasm, but may also be related to other factors and circumstances.
- Drug tolerance is a possible factor in patients with both progressive and nonprogressive disease.

Other factors affecting spasticity and spasms such as urinary tract infections, wounds, pressure sores, other medical conditions, physical therapy, orthoses, drugs influencing spasticity or spasms, and whether contractures were present were also evaluated as these could influence the measurements as well as the dose of intrathecal baclofen. Zahavi et al. stated that none of these factors was considered to have a significant effect on treatment outcomes (no data reported).

There were no significant differences between patients with MS versus a nonprogressive disorder at baseline, 26 weeks and at final assessment (data not reported by authors) though sample size was not large enough to test significant differences.

There was a borderline significant difference ($p=0.05$) in the mean or maximum intrathecal baclofen dose between patients with MS or nonprogressive disease. It is likely that a larger sample size would have allowed the significance level to be more appropriately assessed.

Limitations to the study by Zahavi et al. include:

- An attrition rate of 45% (only 21 of the original 38 patients could be evaluated). An intent to treat analysis was not discussed.
- The current study and the original study had different investigators recording measurements.
- Several patients particularly those with MS had cerebral symptoms such as cognitive dysfunction at followup. Cognitive abilities were also reduced in the elderly patients, who comprised a significant proportion of the study group. Help from family members and caretakers was needed and this may have influenced some results.
- The progressive nature of the disease may have affected the results of the perceived health status. More than half of the patients were >50 years old which may explain why no change was observed in the physical aspects of perceived health status. The psychosocial dimensions are not only related to achieving adequate control of spasticity and spasm, but may also be related to other factors and circumstances.
- Small sample size.
- In some patients care was taken not to abolish muscle tone completely on the premise that patients may be able to use their extensor tone for transferring. Three patients could still make use of their extensor tone in this way and the dose was therefore adjusted in these cases, leading to a lower dose being given.
- Drug tolerance is a possible factor in patients with both progressive and non-progressive disease.
- The sample included a mix of patients who were quadriplegic and diplegic.

■ Plassat et al.(25) conducted a retrospective case series (N=40) to analyze the long- term safety and efficacy of intrathecal baclofen (Level 4 evidence). Forty-one patients who were implanted between 1988 to 2001 were recruited into the study. All patients had severe and intractable spasticity (Ashworth score $\geq$3) and were not relieved by maximal doses of oral medications, or experienced unacceptable side effects. The origin of spasticity was as follows (Table 17):

Table 17. Origin of Spasticity

Spinal Origin n=33		Central Origin n=8	
Traumatic	n=17	Cerebral palsy	n=3
MS	n=6	Anoxia	n=2
Hereditary	n=4	Cerebrovascular	n=3
Tumoural	n=4		
Infectious	n=3		

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In total, 29 patients were clinically examined. Three patients had died. Seven patients were interviewed by telephone. If they were unable to answer the questionnaire due to cognitive deficits, information was obtained from relatives or caregivers. One patient was unable to answer the questionnaire or be clinically examined. Plasset et al. defined the followup duration as the period of time between implantation and assessment, pump withdrawal or death.

Procedure

All patients responded to the test dose injections before pump implantation. The average effective test dose of baclofen was 100.5$\pm$84.34 ug per day for spinal diseases and 143.5$\pm$197.32 ug per day for spasticity of cerebral origin. In all, 57.5% of the implanted pumps were programmable, 22.5% were constant infusion pumps and 20% were manually operated.

Followup
Patients were followed for an average duration of 4 years after pump implantation. The average maximal dose used was 476±260.5 ug per day.

During the first year, the required doses "increased by an average factor of 2.8". From the second year onwards, an increasing proportion of patients reached a stable dose with the proportion rising to include 86% of patients at the end of the 5th year.

Pump replacement was performed 1.4 times per patient due to a complication in two-thirds of cases.

The original Ashworth score before implantation was always ≥3 (no further data provided) and the average score at the final assessment was 1.8±0.6 (n=27) (no p value provided).

Eighty-five percent of the patients would have undergone the procedure again if they had to make the decision. In 85% of patients, the ambulation status was unchanged.

Pharmacological Complications
Common side effects occurred in 54% (20 patients). The most frequent were drowsiness, somnolence, nausea and vomiting.

Twelve percent of patients experienced severe side effects; 80% of these were directly related to pump refill procedures. They included:

n=2 Respiratory arrest due to accidental overinfusion after pump refill
n=1 Overinfusion (profound flaccidity, sedation and vomiting) due to manual pump malfunction
n=1 Mild respiratory depression after a morphine test because of baclofen tolerance.
n=1 Malignant hyperthermia with multivisceral failure and death a few hours after pump refill.

Device Complications

In total, 62.5% of the patients experienced an episode of malfunction, 90% of them required surgical intervention, and 47.5% required more than 1 intervention. The total rate of device malfunctions was 0.2 per year (31 device malfunctions/153 years of treatment). Table 18 gives details of complications; catheters were involved in 58% and pumps in 42% of cases. Pump complications were confined to manual pumps, except in one case where the malfunction of a constant infusion pump was probably caused by unusually warm outside temperature.

Table 18: Catheter and pump incidents.

Catheter n=18		Pump n=13	
Disconnection	n=4	Disconnection of reservoir	n=2
Migration	n=4	Porosity of membrane	n=2
Kinks	n=3	Subcutaneous collection	n=5
Obstruction	n=3	Unexplained	n=4
Fibrosis	n=3		
Others	n=1		

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The pump was removed and intrathecal baclofen stopped in 7 patients (17.5% of cases). The cause was sepsis in 3 cases, baclofen overinfusion in 1, intolerable side effects in 1 and lack of use of manual pumps

in 2 cases.

Limitations to the study by Passat et al. included:
- Retrospective case series design.

■ In the United States, Bjornson et al.(26) used a convenience sample of 30 patients for a pilot study to examine the oral motor, communication and nutritional status of children with **spasticity of cerebral origin** during intrathecal baclofen therapy (Level 3 evidence). One interviewer administered a structured in-person interview tool, data from which were collapsed into 4 change categories: Communication and speech, feeding and nutrition, oral motor function, and gastrointestinal function. Functional severity was ranked with the Gross Motor Function Classification System (GMFCS).

The average time since implantation of the pump at the time of the study was 2.1 years (range 0.3 to 5.3 years). The average dose was 447 ug (range 91 to 1060 ug). The baseline lower extremity Ashworth score was 2.5 (range 2.1 to 2.8). At the time of the study, all patients had responded well to intrathecal baclofen in terms of reduced spasticity with an average change in lower extremity Ashworth score of 0.9 (range 0.7 to 1.1).

Communication and Speech
Of the 23 children capable of speech production, 10 reported improvements.

Feeding and Nutrition
The appetite question was applicable to 26 children in the study, with 10 reporting improvements in appetite since starting intrathecal baclofen. The question was considered not applicable by the caregivers of 4 children who were totally dependent on gastrostomy tubes for nutrition.

Oral Motor Function
Saliva control was applicable to 26 children, with 10 caregivers noting improvement and 8 noting a worse status after intrathecal baclofen. Nineteen children were capable of cup drinking, with 12 improved after intrathecal baclofen.

Gastrointestinal Function
Stool frequency was applicable to all children, and 14 reported a decrease in frequency after intrathecal baclofen. Eight children had an increase in stool frequency. All 30 children or caregivers reported on stool consistency, with harder stools in 11 children and softer stools in 7 children. From comments reported in the questionnaire it appeared that the changes in frequency and consistency represented the occurrence of constipation (infrequent, hard, difficult-to-pass bowel movements).

There were no consistent changes reported in feeding time, ability to orally feed, chewing, swallowing, gagging, nutritional supplements or ability to handle liquids of different densities.

Limitations to the study by Bjornson et al. (26) included:
- Case series design pilot study.
- The variability in results may be partly attributable to variation in priorities about the importance of these issues from one child and family to the next.

■ Dario et al. (2) examined 20 patients with chronic intractable spasticity who received an implantable intrathecal baclofen pump. Spasticity was caused by MS in 14 patients and by spinal trauma in 6 patients.

Clinical efficacy of intrathecal baclofen was evaluated by using the Ashworth Scale, the Spasm

Frequency Scale (SFS), and the Functional Independence Measure (FIM). All parameters were assessed before intrathecal therapy and every 6 months after pump implantation.

At last followup, (mean 24.7 months, range 12-46 months), the mean scores were as follows:

Ashworth score	preoperative 4.3±0.6 postoperative 1.7±0.7, p<0.01
SFS	preoperative 2.4±0.5 postoperative 0.5±0.7, p<0.01
FIM	preoperative 35.7±9.6 postoperative 57.8±12.7, p<0.05

Eighteen patients (90%) stated that they would have their implants again, but 2 (10%) would not.

Limitations to Dario et al. (2) included:
- Small case series design.

■ Fitzgerald et al.(27) examined 52 spastic tetraparetic children within a continuous intrathecal baclofen infusion programme (CIBI).

At entry to the study, 17 of the 52 implanted patients could walk short distances with a frame or assistance, a further 7 could bear weight but not walk, while 28 had no use of upper or lower limbs. Most children were totally wheelchair dependent. Approximately one third had mainstream cognition, the remainder having various degrees of learning disability. Of the 52 implanted patients, 48 (92%) had CP in association with premature birth. One patient was dystonic and the remaining 3 had suffered cerebral insults through drowning, trauma and non-accidental injury. Their ages ranged from 2.5 to 17 years.

Adverse Events
The optimum dose ranged from 50 to 900 ug/day. No adverse events occurred during the refill procedures. The most common problem was catheter migration or fracture.

Outcome
- In all 49 other cases, carers reported improvements in nursing care. All of these saw a reduction in spasticity and an improved range of motion in unfixed joints. Of the 17 who were ambulant prior to treatment, walking was improved in 9 cases. One previously nonambulant patient began to mobilize with walking aids.
- Anecdotal observations:
    - Improvements in speech, swallowing, drooling and upper limb function.
    - Many children appeared to become more socially interactive.
    - Weight gain.
    - Increase in seizures in a small number of children, but the authors believed this to be related to weight gain after CIBI and subsequent subtherapeutic concentrations of anticonvulsants.
    - 2 children with progressive scolioses saw deformities improved; but 2 further cases had progression of deformities. The authors were unable to say whether baclofen had any impact on the rate of progression of mobile deformities.

Fitzgerald et al. stated that a prospective multicentre RCT for both spastic tetraplegics and ambulant children centred at the Queens Medical Centre in Nottingham received approval and is currently underway.

Limitations to the study by Fitzgerald et al. (27) included:
- Case series design (Level 3 evidence).

■ Gooch et al.(28) performed retrospective chart reviews to examine the device and major nondevice-related complications in a group of 100 consecutive patients who received 117 intrathecal baclofen pumps for the management of severe spasticity.

Twenty-four patients (24%) had a total of 48 complications. Several patients had more than one complication (5 patients had 2 complications, 6 had 3 complications, 1 had 4 complications, and 1 had 5 complications). The followup period after pump placement ranged from 6 months to 5.6 years.

The most frequent complication was catheter disconnection, i.e., a disconnection of the catheter at its connection point to the pump. Catheter disconnection was more common in patients using pumps with catheter access ports than in those who had pumps without ports. Ten disconnections occurred in the 62 pumps (16%) with catheter access ports. One disconnection occurred in the 55 pumps without catheter access ports (2%), p=0.02.

Seven of the 50 pumps with 1-piece catheters had disconnections (14%). Four of the 67 pumps with 2-piece catheters had disconnections (16%), p>0.05.

Catheter dislodgement from the intrathecal space was the second most common complication and occurred in 10 cases (8% of pumps implanted). Eight of the dislodgements were in the 62 pumps with catheter access ports (13%) and 2 were in the 55 pumps without (4%), p>0.05. Seven of the 50 pumps with 1-piece catheters had dislodgements (14%) and 3 of the 61 pumps with 2-piece catheters had dislodgements (4%), p=0.05.

Limitations to the study by Gooch et al. (28) included:
- Retrospective case series chart review (Level 4 evidence).

■ Staal et al.(29) retrospectively studied QoL, complication rates, and length of intrathecal baclofen treatment as reported on surveys sent to 56 patients in a community-based rehabilitation centre outpatient clinic (Level 4 evidence). Forty-nine patients responded; 30 adults and 19 pediatric patients. Thirty-six patients (73%) had been using the pump for more than 1 year.

Patients had the following diagnoses: Brain injury (n=11), SCI (n=14), CP (n=22), MS (n=4). One respondent had both CP and SCI and 2 had both brain injury and SCI.

Forty-three respondents (88%) stated they felt the quality of their lives had improved.

Nineteen patients cited complications with their pumps. These included "other" complications (n=11), infection (n=5), catheter dislocation/breakage (n=5), and premature battery failure (n=2). Comments in the "other" category included:
- Increased spasticity when baclofen was low near a refill date and when the pump was empty (n=4)
- Pump "flipped" (n=2)
- Vomiting/headache/weight loss (n=1)

- Itching before pump refill dates (n=2)
- Alarm did not sound near refill date (n=1)
- "Bad reaction the day of a refill that nearly caused convulsions" (n=1)

Despite the complications, 46/49 patients said they would recommend intrathecal baclofen to others. Three patients did not respond to the question.

Limitations to the study by Staal et al.(29) included:
- Retrospective survey.
- Incorrect calculations.

Points of Uncertainty in the Studies of Intrathecal Baclofen for Spasticity Include:

- Not consistently demonstrated in all studies that patients are refractory to all prior 1st line forms of treatment. Some authors (e.g., Shakespeare et al.(30))pointed out there have been no direct head to head comparisons of many first-line treatments.
- Unclear how long a patient can stay on intrathecal baclofen, especially considering that the dose increases due to tolerance.
- Unclear how long intrathecal baclofen can delay contractures and future surgical procedures.
- Lack of quantitative, objective data to determine if nursing care/patient transportation/quality of life/activities of daily living are improved.
- Lack of firm guidelines for treatment of different kinds of spasticity:
    - MS versus CP versus SCI
    - Lower verus upper versus combined upper and lower spasticity
- Lack of published direct head-to-head comparisons of intrathecal baclofen versus alternate technology (except the 1995 Albright et al. (31) study comparing intrathecal baclofen to selective dorsal rhizotomy) (See next section).
- Several reports show a reduction in spasticity with intrathecal baclofen treatment, but none explicitly demonstrate quantitative objective improvements in range of motion in the upper limbs or signs of improved functional skills in comparative trials.

Intrathecal Baclofen Versus Selective Dorsal Rhizotomy

In 1995, Albright et al.(31) conducted a retrospective observational study to compare intrathecal baclofen (n=38) with selective dorsal rhizotomy (SDR) (n=38) on upper extremity spasticity (Ashworth scale) and range of motion in children with CP.

Intrathecal baclofen was recommended for 2 groups of spasticity patients:
1. Functional patients who utilized their spasticity to stand or walk, and who might lose ambulation if their spasticity was eliminated by SDR. The goal of treatment was to improve function.
2. Severely affected children with spastic quadriparesis whose upper extremity spasticity was as severe as the lower extremity spasticity. The goal of treatment was to facilitate care.

SDR was recommended for children with:
1. Spastic diplegia, many of whom were ambulatory, with or without assistive devices. The goal of treatment was to improve gait.
2. Severely affected children with spastic quadriparesis whose upper extremity spasticity was less

than it was in the lower extremities. The goal of treatment was to facilitate care.

The baclofen doses in the functional patients were titrated to reduce lower extremity spasticity without a deterioration of gait and in the nonfunctional patients the doses were titrated so that lower extremity spasticity was reduced to an extent such that it did not interfere with patient care. Intrathecal baclofen doses were not altered according to upper extremity tone. Postoperatively, all patients were examined at 3, 6, and 12 months and yearly afterwards. Spasticity was assessed by a neurosurgeon and range of motion was measured by an occupational therapist. Examiners were not blinded to the treatment.

Albright et al. (31) reviewed the charts of the first 38 patients with cerebral spasticity who had been treated with intrathecal baclofen for at least 6 months, and matched them with 38 patients who had been treated with SDR during the past 8 years. Patients were matched according to pretreatment upper extremity muscle tone (Ashworth scale) and functional status (nonfunctional if they were incapable of independent self-care, and as functional if they were capable of self-care; functional patients were further categorized as ambulatory or nonambulatory) (Table 19).

Table 19: Mean (standard deviation) upper extremity Ashworth Scale score.

Mean upper extremity Ashworth scale	Baseline	6 Months	1 year	P value (baseline to 1 year)
Intrathecal baclofen	2.07±0.82	1.84*	1.66*	<0.001
SDR	2.03±0.74	1.78*	1.7?**	<0.005
	P=0.86			

*Standard deviation not reported
*Second decimal place not reported.
From: Albright AL, Barry MJ, Fasick MP, Janosky J. Effects of continuous intrathecal baclofen infusion and selective posterior rhizotomy on upper extremity spasticity. Pediatr Neurosurg 1995; 23:82-85.

In patients treated by SDR, there was a correlation between baseline upper extremity score and reduction in tone ($p<0.001$). "Patients with a baseline score of 3 were more likely to have a 1 point reduction than those with a baseline score of 2." (Table 19)

In the SDR group, an average of 45.5% of the posterior rootlets were divided, (range 24.9% to 75%). The percentage of posterior rootlets divided did not correlate significantly with the reduction in upper extremity spasticity ($p=0.117$).

There was no significant difference in the reduction of spasticity between functional and nonfunctional patients in either the intrathecal baclofen or SDR group (p values not reported).

There were no significant changes in range of motion in any upper extremity joint, either 6 or 12 months after either intrathecal baclofen or SDR.

The families in both patient groups subjectively reported positive effects in hand function, activities of daily living, speech and mobility.

Limitations to the study by Albright et al. (31) included:
- No a priori sample size estimate/justification.
- Patient groups that had different treatment goals.
- Inappropriate statistics. The Ashworth scale is a nominal scoring system 1-5. It is unclear why the authors performed calculations for continuous data.
- Combinations of inter and intra-group statistics.

- Inconsistent reporting of data. Standard deviation only reported for baseline data.
- Subjective data on hand function, activities of daily living, speech and mobility.
- Patient groups were treated at different times.

Studies of SDR and Rates of Orthopedic Surgery in Patients with CP

■ Chicoine et al.(32) retrospectively analyzed 178 children with spastic CP who underwent SDR between the ages of 2 and 19 years during 1987 to 1991. The patients' disabilities included:

n=58 spastic quadriplegia (33%)
n=116 spastic diplegia (65%)
n=4 spastic hemiplegia (2%)

Patients received physical therapy for a minimum of 6 months postoperatively. Followup intervals after SDR ranged from 24 to 70 months (mean 44 months).

Preoperative clinical assessments, postoperative followup visits and telephone discussions with parents and health care providers were used to document orthopedic surgery performed before and after SDR. Orthopedic operations were categorized as adductor releases, heel cord releases, iliopsoas releases, hamstring releases, femoral osteotomies, ankle/foot osteotomies or "other" (e.g., peroneal muscle tendon transfers and releases, iliotibial band releases, partial patella resections, quadriceps muscle releases, and plantar fasciotomies).

Because the literature contains no historical control for the rate of orthopedic surgery in children with spastic CP, Chicoine et al. divided the patients into 2 groups. Group 1 consisted of 54 patients who underwent SDR between 2 and 4 years of age, and Group 2 consisted of 124 patients who underwent SDR between 5 and 19 years of age. A comparison of these 2 groups was used to assess the effect of early versus late SDR on the lifetime rates of orthopedic surgery.

Overall, at the time of last followup, 68 (38%) of 178 patients in the study had undergone at least one orthopedic operation before and/or after SDR, with a rate of 22% in Group 1 and 45% in Group 2.

The overall orthopedic surgery rate was higher for Group 2 than Group 1 ($p=0.037$).

Limitations to the study by Chicoine et al. include:
- Retrospective case series study design.
- The average rate at which orthopedic operations are performed in children with spastic CP depends on many variables including the distribution of CP types and the age of patients. Additional factors complicating such analysis include disagreement among orthopedists as to the optimum age for surgical intervention.
- In the Kaplan-Meier plots for Group 1 versus Group 2 for overall operative rates, the trend is for the 2 plots to merge together. This may reflect that some of the operations were typically performed at a later age for Group 1 compared to Group 2. In addition, this may reflect some clinicians' decisions to postpone orthopedic surgery until the child's outcome from SDR is ore clearly defined. Therefore, the overall rates of orthopedic surgery may not be lower for Group 1, but merely postponed until later in the life of the child.

Studies of Intrathecal Baclofen and Rates of Orthopedic Surgery in Patients with CP

■ Gerszten et al.(33) retrospectively reviewed the outcomes of 48 patients with spastic CP who were treated with intrathecal baclofen in order to assess the need for orthopedic surgery of the lower extremities in these patients.

The patients' ages ranged from 5 to 43 years (mean 15 years). The mean followup was 53 months. The diagnoses included 8 cases of spastic diplegia (16%) and 40 cases of spastic quadriplegia (84%). Patients whose average lower extremity muscle tone decreased by 1 or more according to the Ashworth scale after any intrathecal baclofen dose (50, 75, or 100 ug bolus injection) were considered to have a clinically significant response and were offered implantation of a continuous infusion pump. The mean baclofen dose was 306 ug/day (range 25-1350 ug/day).

After pump implantation , baclofen doses were increased during the first week until the mean lower extremity muscle tone was perceptibly reduced and then increased again during the followup period titrating the dose to the desired clinical response. Most patients received physical therapy 2-5 days per week for the first 6 months postoperatively and 1-3 days per week for the next 6 to 18 months.

Documentation of orthopedic surgery performed before and after baclofen pump placement was obtained from preoperative clinical assessments and postoperative followup visits.

Twenty-nine patients (60%) had undergone at least one orthopedic procedure before baclofen pump placement. The mean patient age at the time of the first orthopedic procedure was 8 years old (range 2-19 years).

Subsequent surgery was planned at the time of pump placement in 28 patients (58%), however, 10 patients (36% of those in whom surgery was planned) eventually underwent orthopedic surgery after intrathecal baclofen implantation. Further analysis of this group of 10 patients revealed that in all cases, the surgical procedure was planned at the time of initial evaluation for intrathecal baclofen therapy. The mean age for this group of patients was 10 years (range 5-19 years). Of the 10 operations, 8 were performed within 12 months and 2 within 18 months of pump placement. No patient who underwent surgery after intrathecal baclofen therapy required a second operation.

In the remaining 18 (64%) of 28 patients who did not subsequently undergo their planned surgery, the same orthopedic surgeon believed that intervention was no longer required. This decision was based on the degree of diminution of contractures such that joint range of m had improved and no significant functional limitations were present.

The authors suggested that "Although improvement in spasticity does not result directly in improvement of lower extremity contractures, dislocation or deformities, it may result in reduction of apparently fixed contractures that in reality are dynamic contractures."

Eleven patients (23%) required a revision of their pump for malfunction secondary to catheter-related problems, including catheter fracture and catheter dislocation. Gerszten et al. stated that the initial thin walled intrathecal catheter was redesigned and no further fracture occurred with the current thicker-walled catheter.

Limitations to the study by Gerszten et al.(33) included:

- Retrospective case series design.
- No historical control group exists for the rate of surgery in patients with spastic CP.

- Given the wide range of ages, it cannot be determined if intrathecal baclofen therapy at an earlier age has greater benefit over pump placement at a later age for a reduction in the development of lower extremity orthopedic deformities that result from spasticity.
- The number of patients who avoided procedures that may require surgery in the future is not known.
- Lack of a control group undergoing physical therapy intervention.

Given the lack of high/moderate quality evidence for the use of intrathecal baclofen for spasticity, it was decided that the previously mentioned alternatives for the treatment of spasticity would also be examined.

Cochrane Review: Antispasticity agents for Multiple Sclerosis (Shakespeare et al.(30))

Shakespeare et al.(30) conducted a systematic review of the absolute and comparative efficacy and tolerability of **antispasticity agents for MS**. A literature search identified articles up to June 2003. Drugs included in the analysis were: baclofen, dantrolene, tizanidine, botulinum toxin, vigabatrin, prazepam, threonine and cannabinoids. Intrathecal baclofen was not one of the drugs included in the analysis.

All of the studies that were included in the systematic review by Beard et al (18) were also included in the analysis by Shakespeare et al.

Main Results

- In total, 26 placebo controlled studies and 13 comparative studies met the selection criteria and were included in this review.
- Fifteen of these studies used the Ashworth scale, of which only 3 of the 8 placebo-controlled trials and none of the 7 comparative studies showed a statistically significant difference between test drugs.
- Spasms, other symptoms and overall impressions were only assessed using unvalidated scores, and results of functional assessments were inconclusive.

Conclusion

- The variability of spasticity and the lack of a sensitive reliable, functional and symptomatically relevant assessment tool for spasticity, contributed to the inconclusive results of placebo-controlled trials attempting to document the efficacy of antispasticity agents currently in widespread use.
- Comparative studies have been similarly inconclusive.
- *"No firm recommendations to change practice can be made from this systematic review and in particular there is no good evidence to prefer newer over older agents."*

Shakespeare et al.(30) noted serious limitations to the studies:

- When considering the problem of spasticity, it is clear that both our understanding of the problem and our ability to measure it are seriously deficient. This is reflected in the wide variety of approaches taken to assess spasticity in the trials reviewed and the inconclusive objective results of the vast majority of the trials.
- Difficulty remains in demonstrating the efficacy of the active drug against placebo.
- There remains a gap between published evidence and the daily experience of those who manage spasticity. Better assessment tools are needed to confirm the clinical impression that the widely used antispasticity drugs (baclofen, dantrolene, tizanidine) are more effective than placebo.
- The validity of the Ashworth scale -the only widely used assessment tool for spasticity- has been seriously questioned and Shakespeare et al. were not aware of any validated method of assessing

spasm scores. Sixteen of the studies summarized reported an "Ashworth scale" but used different methods to assess and score the Ashworth scale results, so a meta-analysis was not attempted.

- Only 3 of the 8 included placebo-controlled trials that reported Ashworth scale results showed a statistically significant superior effect of active drug over placebo. None of the comparative studies were able to show a statistical difference between the trial drugs.
- The concept of weakness reported by patients with spasticity is poorly characterized. Evidence for differences between drugs was limited to limb power scores using unvalidated measures.(30)
- The decision to treat a patient with antispasticity medication is made for different reasons in different patients:
    - The immobile patient is treated for symptomatic relief and in order to make nursing care and seating easier, whereas the ambulant patient is treated with the additional aim of improving or preserving mobility.
    - The diagnostic examination of the neurologist is not always an adequate predictor of the functional examination of the physiotherapist or the daily experience of the patient.
    - The currently available evidence does not help to answer the question of which agents are best for treating different spasticity scenarios.

National Health Service Research and Development (NHS R&D), United Kingdom, 2003: Treatments for Spasticity in MS

Beard et al. (18) conducted a systematic review of all treatments for spasticity in MS. Intrathecal baclofen was previously discussed in detail, and below is a review of the alternative treatments

a) Phenol

Phenol injection into or around a nerve produces a temporary block that may last for months to control muscle spasticity.

Beard et al. did not identify any controlled studies of the effect of phenol injection on spasticity, either in MS or due to other causes. One controlled study was identified which compared the effect of 2 different approaches to obtuator nerve block in patients with adductor spasticity, but this study was small and appeared to use unvalidated outcome scales. Beard et al. stated that its greatest value may be as a case series documenting the effect of obturator blockade, irrespective of approach used.

Four case series were identified which included patients with MS (although sometimes the number with MS was not reported). Few details were given about the patients included in the studies, or how they were selected, other than that they suffered from spasticity.

Summary of the direction of effect and impact on function:

- All of the case series reported relief of spasticity in a high proportion of cases.

Side effects

- Few side effects were reported in the case series.
- Complications reported included: "further muscle weakness", sensory loss and genitourinary dysfunction following subarachnoid block.
- Peripheral nerve blockade other than the obturator nerve is reported to result in "anesthetic skin" and sometimes persistent severe pain.
- Arachnoiditis and sphincter dysfunction following intrathecal injection are also reported.

Summary

- The evidence of effectiveness of phenol blockade in treating spasticity was provided from case series study designs. However, due to "the stable or deteriorating nature of spasticity and the prompt relief observed in a high proportion of cases, it is reasonable to conclude that phenol injections do relieve spasticity with a duration of action of some months."
- There is insufficient evidence to draw conclusions about the functional impact of phenol for spasticity.

b) Botulinum Toxin

Five Botulinum toxin (**BT)** papers met the inclusion criteria for the analysis. All patients in the selected studies had chronic or severe spasticity and in many cases were nonambulant. Two studies recruited only patients with MS.

Details of the included studies examining BT for spasticity are provided in Table 20.

Summary

- Although BT is not licensed in the UK for the treatment of spasticity in MS, there is evidence that it is effective.
- Its role is restricted to those cases where the relief of spasticity is of greater functional benefit than retaining any muscle strength.
- "In practice, this is likely to be the most severely disabled patients."

Table 20: Studies examining the use of botulinum toxin for spasticity included in the NHS R&D review

Study	Design	Drugs and Dose	Patients	Withdrawals	Outcomes measured	Results
Snow et al. (1990) Canada	Double-blind placebo controlled crossover RCT	BT 160 ng (400 units) i.m. in 3 muscle groups. 6 weeks	N=10 Mean age 40 years (23-61) All had stable MS. Nonambulant. Recruited from long stay institutions.	N=1 on placebo	Adapted Ashworth scale. Spasm Frequency score Hygiene score	BT showed **significant reduction in spasticity over placebo (p=0.009).** Frequency score in BT group decreased from mean 2.9 to 2.7, not significant. **Statistically significant improvement in BT group in hygiene score (p=0.009)**. No change in hygiene score for placebo group. Greatest benefit found in most severely affected patients. No adverse effects noted.
Grazko et al. (1995) USA	Double blind placebo controlled crossover RCT	BT 25-250 units. Placebo Treatment 2 given 2 weeks after treatment 1 or when any clinical effect had worn off.	Total N=20, of whom 12 had spasticity and of these 5 had MS. Ages 40-66 years Baseline Ashworth score 3-4+	N=0	Modified Ashworth Scale	Reduction of at least 2 grades on the Ashworth score in all 5 patients with MS lasting 1-3 months. "Subjective improvements in movement and posture"
Cava (1995) USA	Open trial. Patients were followed up every 2 weeks, but the total duration of the study is not clear. Duration of effect was found to be 3-6 months.	BT. Intramuscular dose per muscle varied from 40 to 180 units. Maximum dose range 270-300 units.	N=16, 10 of whom had MS (MS patients who had taken corticosteroids in previous 6 months excluded) All >18 years All had dysfunctional limb spasticity but no details of functional status.	N=0	Modified Ashworth scale Frequency of spasm scale Pain scale	13/16 patients (8/10 MS patients)showed significant improvements. There was no change in 3 patients (2/3 were MS patients). Mean Ashworth score changed from 2.6 to 1.3. This change was statistically significant (P value?) Spasm frequency also declined but it was not statistically significant. There was a large reduction in pain particularly in the MS patients (p value?). Adverse effects were minimal, mainly temporary bruising.
Finsterer et al. (1997) Austria	Prospective, open label uncontrolled longitudinal with followup after 17-57 days after initial injection.	BT mean intramuscular does per patient 276 units. Mean dose per muscle 116 units. 3 of the patients had a booster dose owing to lack of response	N=9 Mean age of MS patients =52 years. 5 had severe spasticity. 3 had right upper or lower limb spasticity and 1 had	N=0	Turn/amplitude analysis (EMG measure) Activities of daily living. Pain. Muscle tone (Ashworth scale) Range of motion.	All outcome measures were assessed on a 5 point scale by the physician, not the patient. The duration of followup varied. There is no evidence that this scoring system has any validity. All 5 MS patients showed an improvement in TAA, mostly by at least 2 points. 4/5 MS patients showed an improvement of 1 point (Activities of daily living). 4/5 MS patients an improvement in pain.

		initially, the number of muscles treated was between one and five. Muscles were selected for injection if their Turn/amplitude analysis (TAA) was >150.	tetraspasticity. The spasticity was due to MS in 5 cases. Average duration of spasticity in MS cases was 16 years.			3/5 MS patients showed an improvement (Ashworth scale). MS patients showed an improvement in range of motion. Scores for all patients improved at a statistically significant level. Improvement did not appear to be dose dependent. Injection was tolerated by all patients without complaint and there were no major side effects.
Hyman et al. (2000) UK	Double blind placebo controlled dose ranging RCT	BT 500 (n=21) 1000 (n=20) 1500 (n=17) units or placebo (n=16). Single treatment (both legs only)	N=74. All with probable or definite MS with disabling spasticity of hip adductors, Kurtzke Expanded Disability Status $\geq$7, stable for 6 months, moderate pain, or difficulty in nursing, hygiene score $\geq$2. Mean duration of MS 16-23 years. Mean ages 47-54 years. Concomitant medication continued.	N=2 prior to week 4, N=14 prior to end of study at week 12, due to need for re-treatment.	Modified Ashworth score (muscle tone x spasm frequency). Upper leg pain (4 point scale). Clinical global rating (4 point scale). Perineal hygiene score (6 point scale). Time to re-treatment. Primary analysis was performed on the change from baseline at week 4.	Improved in all groups; no difference between groups although in placebo group, the improvement was due to a reduction in spasm frequency only, with no reduction in tone. Proportion pain free increased in all groups, no difference between groups. Median rating improved from severe to moderate n all groups. Median score unchanged in placebo and 500Unit groups; improved from 2 (one person able to clean/catheterise with effort) to 1 (the same, with ease) in 1000-and 1500 Unit groups. Median time to re-treatment 56, 99, 111, 119 days in placebo (n=7), 500-Unit (n=8), 1000-Unit (n=10), 1500-Unit (n=9) groups respectively (p=0.015). Adverse events reported in 55% of patients on active treatment, 63% on placebo.

Table reproduced with permission from the NCCHTA; From Beard S, Hunn A, Wight J. Treatments for spasticity and pain in multiple sclerosis: a systematic review. [Review] [154 refs]. Health Technology Assessment (Winchester, England) 2003; 7(40):iii, ix.

c) Oral Drugs for Spasticity

Beard et al. (18) stated that there is limited evidence of the effectiveness of 4 oral drugs for spasticity (baclofen, dantrolene, diazepam and tizanidine). "All appear to be approximately equally effective when assessed clinically, though in no case is there any good evidence of functional benefit."(18)

d) Non-Drug Therapies for Spasticity

Beard et al reviewed the following non-drug therapies that are used to treat spasticity in MS:

Neurotomy
- There is anecdotal evidence that selective neurotomy can be helpful in reducing spasticity only when the spasticity affects just a single joint.

Myelotomy
- There is anecdotal evidence of a good success rate but the procedure is not reversible.
- Little or no evidence in patients with MS.

Chronic cerebellar stimulation (CCS)
- A review of CCS, which is used to reduce spasticity caused by CP, found that CCS resulted in an 85% reduction in spasticity. How the change in spasticity was measured was not reported.

Overall Conclusions of NHS R&D Review of General Treatments for Spasticity in MS
- Overall, there is limited evidence for the effectiveness of oral therapies for moderate spasticity.
- The findings of this review are supported by reviews of the same treatments for spasticity derived from other etiologies.
    - It is unclear whether or not the effectiveness of treatments for spasticity of etiologies other than MS, such as SCI or stroke, can be compared.
    - The evidence from other reviews suggests that the effectiveness of oral antispasticity agents is very weak, despite their widespread use.
- *"The evidence for intrathecal baclofen treatment is stronger*. It is believed that the appropriate use of intrathecal baclofen could result in significant savings in hospitalization costs in relation to bedbound patients who are at risk of developing pressure sores." To date, no formal economic analysis has been conducted to provide evidence for this claim. (18)
- There is a need for more research into the clinical and cost-effectiveness of treatments for spasticity in MS, including the development of better outcome measures which relate to functional ability and patients' QoL.

Systematic Reviews on the Use of Botulinum Toxin for Spasticity

Canadian Coordinating Office for Health Technology Assessment (CCOHTA), February 2005

BT inhibits the release of acetylcholine (a neurotransmitter) from the neuron, resulting in muscle relaxation. It is injected directly into affected muscles. The dose generally depends on which muscle is being injected. Repeat doses may be needed because the pharmacologic effect of BT usually lasts 2 to 4 months. BT differs from generalized pharmacotherapy (baclofen) and surgery (SDR) because individual muscles can be directly targeted, depending on the goals of treatment.(34)

Garces et al. (34) conducted a systematic review of BT for upper and lower limb spasticity. The literature review went up to April 2004.

BT is approved in Canada to treat spasticity in patients with CP and stoke.(34)

CCOHTA Results(34)

- Of the 33 RCTs included in the review, 12 focused on patients with stroke, 15 on patients with CP, 2 on patients with MS, and 4 on patients with other disorders.(34)
- Quality scores according to the Jadad scale varied (high=4 trials, moderate=16 trials, low=13 trials) and the techniques used to prevent bias by concealing the allocation sequence were often unclear. Despite the low scores of some trials, (5 single blind trials, 5 trials reported in an abstract), they provided important clinical information.

BT for Upper Limb Spasticity in Patients Post-Stroke

- Nine trials compared BT to placebo.
- Patients receiving BT had decreased muscle tone and increased passive range of motion, but statistically significant differences when compared to placebo were not shown in all studies.
- A meta-analysis of 2 trials examining the effect of BT on wrist muscle tone measured using the Ashworth scale showed a statistically significant difference (weighted mean difference) (Table 21).
- One trial reported increased active range of motion.
- There were no statistically significant differences in adverse events (Table 22).

Table 21: Outcomes for stroke patients after BT treatment that were reported in a manner appropriate for meta-analysis(34)

Outcome Measured	Studies included	Weighted Mean Difference (WMD) and 95% CI	Heterogeneity (p value)
Effect of BT on muscle tone using Ashworth scale at wrist in patients with stroke (fixed-effects model)	Brashear et al. (n=64) Simpson et al. (n=9)	-0.54 (-0.78, -0.30)	P=0.005
Effect of BT on muscle tone using expanded Ashworth scale at elbow in patients with stroke (random effect model)	Bakheit et al. (n=22) Bakheit et al. (n=27)	-6.28 (-16.02, 3.47)	P=0.04
Effect of BT on muscle tone using expanded Ashworth scale at elbow in patients with stroke (fixed-effects model)	Bakheit et al. (n=22) Bakheit et al. (n=27)	-4.65 (-9.02, -0.28)	P=0.04
Effect of BT on muscle tone using expanded Ashworth scale at wrist in patients with stroke (fixed-effects model)	Bakheit et al. (n=22) Bakheit et al. (n=27)	-11.73 (-16.72, -6.74)	0.51
Effect of BT on muscle tone using expanded Ashworth scale at finger in patients with stroke (fixed-effects model)	Bakheit et al. (n=22) Bakheit et al. (n=27)	-7.87 (-13.49, -2.24)	0.58
Effect of BT on passive range of motion at elbow in patients with stroke (fixed-effects model)	Bakheit et al. (n=22) Bakheit et al. (n=27)	2.58 (-6.37, 11.54)	0.16
Effect of BT on passive range of motion at wrist in patients with stroke	Bakheit et al. (n=22) Bakheit et al. (n=27)	9.00 (-0.28, 18.28)	0.78
Effect of BT no active range of	Bakheit et al. (n=22)	-4.29 (-13.83, 5.24)	P=0.21

motion at elbow in patients with stroke (fixed-effects model)	Bakheit et al. (n=27)		
Effect of BT in active range of motion at wrist in patients with stroke (fixed-effects model)	Bakheit et al. (n=22) Bakheit et al. (n=27)	2.03 (-6.80, 10.86)	P=0.49

From: Garces K, McCormick A, McGahan L SB. Botulinum toxin A for upper and lower limb spasticity: a systematic review. 51. 2005. Canadian Coordinating Office for Health Technology Assessment (CCOHTA).

Table 22: Meta-analysis of adverse events in patients with stroke who received BT Treatment(34)

Outcome Measured	Studies Included and Treatment (n/N)	Risk Difference and 95% CI	Heterogeneity (p value)
Adverse effects with BT treatment in patients with stroke	Bakheit et al. (25/63) Bakheit et al. (3/20) Bakheit et al. (20/32)	-0.01 (-0.16, 0.13)	P=0.98

From: Garces K, McCormick A, McGahan L SB. Botulinum toxin A for upper and lower limb spasticity: a systematic review. 51. 2005. Canadian Coordinating Office for Health Technology Assessment (CCOHTA).

Patients with Stroke and Lower Limb Spasticity

- Three trials in total.
- One trial compared BT to phenol (Kirazli and On):
    - Muscle tone was decreased compared to phenol ($p<0.05$)
    - Injections of phenol were reported to be more painful than those of BT
- One trial compared BT to placebo (Pittock et al.):
    - Muscle tone was decreased compared to placebo (at 4 weeks p=0.0002 to 0.0116)
    - Passive and active range of motion was greater in patients receiving BT compared to placebo, but it was not reported whether the difference was statistically significant
    - Walking speed was not significantly different compared with placebo
    - The overall rate of adverse effects was similar to placebo
- One trial compared BT, functional electrical stimulation and physiotherapy to physiotherapy alone (Johnson):
    - Walking speed was significantly faster with BT and physiotherapy compared with physiotherapy alone (p=0.04).

Patients with CP and upper limb spasticity

- Two trials were identified.
- Neither trial reported the overall rate of adverse effects.
- One study showed statistically significant (p=0.04) improvement in the quality of upper extremity skills test (QUEST, a standardized validated test of upper extremity function) (Fehlings et al.).
- One trial compared BT to placebo (Correy et al.):
    - Muscle tone at the elbow and wrist was significantly decreased compared with placebo for at least 2 weeks (p=0.01 and p=0.003 respectively)
    - Active range of motion was significantly greater with BT treatment compared with placebo at 2 weeks
- One trial compared BT and occupational therapy to occupational therapy alone (Fehlings et al.):
    - There were no statistically significant differences in muscle tone in patients receiving BT and occupational therapy compared to occupational therapy alone

Patients with CP and Lower Limb Spasticity

- Thirteen trials were identified.
- Eight trials compared BT to placebo:
    - Three trials reported increases in passive range of motion but statistical significance was inconsistent. Garces et al. stated that the reporting of data did not allow for meta-analysis

of this outcome
- Three trials measured significant differences in active range of motion ($p<0.001$ to $p<0.05$)
- Gait as measured using video gait analysis ($p=0.04$) and a physician rating scale ($p=0.041$ to 0.003) was significantly greater compared to placebo
- Other scales rated by patients, parents or physicians (physician rating scale, questionnaires, Vulpe assessment battery and subjective functional assessment) generally indicated an increased improvement in function compared to placebo ($p<0.01$ to <0.05)
- One trial designed to look specifically at pain, reported a significant difference compared to placebo after adductor release surgery ($p<0.02$ to <0.001)
- When the incidence of adverse events from 3 trials was combined, patients receiving BT experience significantly more adverse events than those receiving placebo. Common adverse events were local pain and weakness (Table 23)

Table 23: Meta-analysis of adverse events in patients with CP who received BT treatment(34)

Outcome Measured	Studies included and Treatment (n/N)	Risk Difference and 95% CI	Heterogeneity (p value)
Adverse effects with BT treatment in patients with CP (fixed-effects model)	Baker et al. (48/94) Komanet al. (12/72) Uhbi et al. (6/22)	0.16 (0.07, 0.25)	P=0.66

From: Garces K, McCormick A, McGahan L SB. Botulinum toxin A for upper and lower limb spasticity: a systematic review. 51. 2005. Canadian Coordinating Office for Health Technology Assessment (CCOHTA).

- Two trials compared BT to casting:
  - No significant difference in tone
  - No significant differences in passive range of motion
- Two trials compared BT to physiotherapy
  - One trial reported a significant ($p<0.05$) decrease in hip adductor and calf tone compared to physiotherapy. However, the scores were only obtained from 8 of the 49 patients
  - No significant differences in passive range of motion
- One trial compared BT to orthosis.
- There were no statistically significant differences in global motor function measure scores between patients receiving BT and placebo, physiotherapy, orthosis or casting.

Patients with MS and Lower Limb Spasticity
- Two trials were identified
- One study reported a significant decrease in tone ($p=0.008$) (Snow et al.). Due to differences in the reporting of muscle tone, the results of the trials could not be combined.
- Significant differences in passive and active range of motion, assessments of function and /or disability and adverse events were not reported.

Patients with Various Diseases and Spasticity
- Four trials were identified.
- A wide range of results were reported and no overall conclusions could be made due to the diverse patient population and treatment protocols.

CCOHTA Conclusion(34)
- BT resulted in decreased muscle tone across most trials and diseases.
- Increased range of motion, improved gait and improved function were shown in many studies, but statistical significance was not always reached.
- Variability in results across studies may be due to the wide variety of disorders studied and the

differences in study designs and outcomes measures used.
    - Combining results was seldom possible
- Adverse events reported in most studies are low in number and often temporary.
- Improved methods of reporting would lead to more robust conclusions about the comparative safety of BT.
- Long-term patient-specific goal-focused outcomes are needed to further define the clinically meaningful improvements in therapeutic outcomes.

Limitations to the CCOHTA Conclusions

- The dose, location and frequency of injection differ among trials based on patients' requirements.
- Additional antispasticity drugs are used in some trials and not in others.
- Muscle tone and range of motion are commonly reported in trials but are not necessarily the most important outcome:
    - Reduction in muscle tone as measured by the Ashworth scale and improvement in joint motion is often achieved, but whether these improvements translate into functional ability is difficult to establish
    - Reliability and validity of the Ashworth and modified Ashworth scale have been explored, however, there is incomplete evidence that these scales reflect spasticity
    - Lower scores on the modified Ashworth scale may not provide a valid measure of spasticity (REF)
    - These scales are ordinal and trial investigators may have used inappropriate statistical tests (REF)
- Few goal-focused patient-specific outcomes (e.g., increasing the use of function of an upper extremity, improving brace fit, preventing contracture, decreasing pain and increasing ease of care.):
    - Goals are patient-specific, and each clinical case is unique such that each patient and family may have different outcome priorities.
- Dose ranging trials have been conducted, but a dose-response relationship is not always evident. The dose used is patient and muscle specific and may depend on such factors as the number of muscles to be injected, severity of spasticity and the patient specific goal to be attained.
    - An increased dose does not always lead to an increased incidence of adverse events in the trials
- Weakness was reported as an adverse effect in some studies and may have been due to BT. Weakness may also have contributed to reports of lack of coordination, abnormal gait, unsteadiness or accidental injury.
- Trials are short-term ranging from 6 to 24 weeks. One trial lasted 12 months. Therefore, long-term effects of repeated BT such as prevention of fixed contractures, prevention of surgical intervention, and long-term improvement in gait or upper extremity function require further analysis.
- Most of the trials involve small numbers of patients and may be underpowered.
- Variability in outcome measures and missing data prevented the pooling of results:
    - Muscle tone is reported using the Ashworth, modified Ashworth and the expanded Ashworth scale
    - Lack of meaningful data for meta-analysis. (i.e., mean difference from baseline and standard deviation). Some trials used median and range or interquartile range. In most cases, the results of 2-3 trials, sometimes by the same author, could be combined
    - In the section describing the evidence of BT in patients with stroke and upper limb spasticity, most outcomes could only be pooled from 2 trials.

Mulligan et al.(35) conducted a systematic review of the efficacy of BT in the treatment of spasticity in ambulant children with CP. Inclusion criteria consisted of RCTs or self- controlled "experimental studies". Patients had to be:

- Children (age range 0-17 years)
- CP
- Ambulant and have lower limb disability affecting gait

Efficacy of intramuscular injection of BT was compared to no intervention, physiotherapy management with and without casting/splinting, and the effect of placebo.

Outcome measures were:

1. Impairment measures of muscle spasticity, length and joint range of motion using the Modified Ashworth Scale, the Modified Tardieu Scale and goniometry.
2. Functional measures of the GMFM and ambulation status
3. Gait analysis using subjective scales, 2-dimensional (video) analysis, 3-dimensional analysis and electromyography

No literature search cut-off date was reported.

The search strategy produced 48 articles. A total of 16 studies met the inclusion criteria. Of these studies, 5 were RCTs and 11 were self-controlled trials. Of the RCTs, 2 compared BT to casting. Saline injections as placebo were compared in the other 3 RCTs.

The review by Mulligan et al. was descriptive and for the results of the RCTs stated:
"While the calibre of these studies was deemed to be high or moderate, the results were not always conclusive as to the efficacy of BT in functional outcome. Change in dorsiflexion through the gait cycle showed the most consistent improvement with BT, with other measures such as gain analysis, other functional measures and spasticity (when measured) did not consistently show significant improvement when compared to casting or placebo."(35)

Mulligan et al. concluded that "BT is effective in temporarily reducing spasticity and allowing a greater range of movement at the ankle to enhance functional improvements in ambulant patients with CP affecting their lower limb function."(35)

Limitations to the study by Mulligan et al. included:

- Variability in reported outcome measures, injection location and concentration. "While there was general consensus that BT has a positive effect on improving function, most of the studies reviewed used multiple outcome measures to determine the effect of BT. This made comparison of article outcomes difficult as each study used a variable mix of common outcomes to measure the effect of BT on children with CP."(35)

■ Boyd et al.(36) conducted a systematic review of the evidence for the use of BT in the management of children with CP.

A literature search was conducted up to December 2000. Inclusion criteria consisted of:

- RCTs of management of the lower limbs using BT with placebo, control or comparison treatment groups.
- Prospective non-RCT of BT in the lower limbs with objective outcome measures.
- Children with CP treated for movement disorders due to spasticity in the lower limbs.
- Intramuscular injection of BT irrespective of dose or muscle injected.

- BT treatments compared to normal saline, casts or physiotherapy through a randomized allocation procedure.

The initial literature search identified 156 papers as having possible relevance to any management of the lower limb in children with CP. Of these, 40 were excluded since they were retrospective or without objective outcome measures. Ten RCTs met the inclusion criteria. Nine studies had concealed allocation and 4 of the 10 had intent-to-treat analysis.

Five of the 10 trials used the physicians rating scale (PRS) as the primary outcome measure. The PRS gives a composite score ranked from 0 (worst score) to 14 (best score). Success was defined a priori as a 2 grade or more increase in the score from the baseline composite score. The number of children in each group who had a successful treatment with either BT or control with placebo injections or casting was collated and the proportion of the total sample calculated.

The results of the treatment effect are reported as a standardized risk difference for all 6 studies using the PRS after BT in the lower limb. All studies used the same standardized outcome measure with the outcome assessed at 6-16 weeks followup and compared to baseline. The mean pooled risk difference for BT and placebo studies was 0.25 (0.13, 0.37) and for BT and casting studies was 0.23 (-0.06, 0.53).

Twenty-five percent more of the BT treated groups would improve by 2 or more points on the PRS compared to the placebo group (pooled sample size n=204). Similar results (although not statistically significant) were observed for the BT groups compared to casting with a pooled risk difference of 0.23 (-0.06 to 0.527) (pooled sample size n=38).

In some studies, different doses of BT were used.(36) The doses of BT in early studies were 2-4 U/kg/muscle. These doses are lower than what Boyd stated was current clinical practice which varies from 7 to 11 U/kg/calf to a high of 9 to 13 /kg/calf or 25.5 U/kg/body weight for children with diplegia.(36) It is unclear whether there is an optimal dose per muscle or per child for longest duration of response and minimization of side effects.(36) When comparing clinical trials it is important to compare dose of BT/kg/muscle, dilution of BT used, and type of BT and re-injection schedules.(36)

It is difficult to compare results of studies using different preparations of BT since some pharmacokinetic studies suggested these have different properties.(37;38) Some studies suggested that 1 U BOTOX may compare to between 3 and 5 U Dysport.(36)

There is no clear evidence of functional changes following BT as measured on gross motor function measure (GMFM) in children treated with BT compared to control groups who received combinations of physiotherapy with or without bracing or casting. There appears to be variability in functional change in these studies according to patient severity, but it is difficult to compare studies reporting either goal scores or total scores on GMFM.(36) The use of the GMFM as a sensitive measure of functional change may create a dilemma for research, as the more mildly impaired children with hemiplegia and diplegia may be the best responders to BT but may often reach a ceiling with the GMFM items.

In a group of children with severe functional impairment (Gross Motor Function Classification System GMFCS Levels III to V), Boyd et al. reported a 6% change in total GMFM scores in both the BT with brace treated and control groups over 12 months. There was a greater difference in goal scores between the treatment and control groups but the difference was not significant. The amount of change in the GMFM total scores over 12 months was greater in the mildly impaired children compared to the more severely impaired children. Boyd et al. stated that these studies highlighted the potential for effect of GMFM in children with severe diplegia or quadriplegia, or the lack of functional change in this group of patients following BT.

Overall, Boyd summarized the current evidence for management of the lower limb in children with CP using a grading system by Sackett.(36)

Grade A Evidence (extensive evaluation):

- Physiotherapy: Several RCTs with equivocal outcomes and a meta-analysis showing a small treatment effect (Ottenbacher et al. 1987).
- SDR: Three large RCTs examined the efficacy of SDR compared to physiotherapy, and a meta-analysis demonstrated the efficacy of SDR (McLaughlin et al., 2000).

Grade B

- Intrathecal baclofen: Two small randomized studies of short term baclofen infusion but no long-term studies.
- Serial casting: Two small short term randomized trials.

Grade C (Prospective studies with objective outcome measures but no RCTs)

- Strengthening
- Orthoses
- Orthopedic surgery

Summary of BT for Treatment of Spasticity

- Level 2 Evidence of effectiveness
- Poor standardization and heterogeneity makes comparisons and summary difficult.
- To date, no-long term studies of outcome for use of BT in children with CP
    - E.g., progression to surgery for ambulant patients and outcome of hip displacement in children with adductor spasticity.
- Interrelationships of BT injections with orthoses, casting or surgery have not been examined in large cohorts.
- There is a need for measurement of outcomes in terms of health related QoL and economic evaluation.

Systematic Reviews on Selective Dorsal Rhizotomy (SDR) for Treatment of Spasticity

McLaughlin et al.(39) conducted a meta-analysis of 3 RCTs that examined children with spastic diplegia who received either SDR plus physiotherapy (SDR + PT) or PT without SDR (PT only). Outcome measures were spasticity (Ashworth scale) and function (Gross Motor Function Measure [GMGM]) up to 1 year after operation.

The literature search identified RCTs up to December 2000. Baseline and 9-12 month outcome data were pooled (N=90 patients).

At baseline, 82 patients were under 8 years old and 65 had Gross Motor Classification System Level II or III disability. Pooled Ashworth data analysis confirmed a reduction of spasticity with SDR+PT (mean change score difference -1.2, $p<0.001$). Pooled GMFM data revealed greater functional improvement with SDR +PT (difference in change score +4.0, $p=0.008$).

Multivariate analysis in the SDR+PT group revealed a direct relationship between percentage of dorsal root tissue transected and functional improvement ($p=0.0002$).

McLaughlin et al.(39) concluded that SDR+PT is efficacious in reducing spasticity in children with spastic diplegia compared to PT alone and has a small positive effect on motor function.

Limitations to the meta-analysis by McLaughlin et al.(39) included:

- Short-term results up to 1 year post surgery.
- Heterogeneity was not calculated or addressed by the authors. *"In each of the 3 original studies, there were not differences in baseline characteristics between treatment groups so the corresponding analysis is not presented here for the pooled data."*
- No discussion of random or fixed effects models.
- No weighting of studies. Summary statistics were calculated using blocked Wilcoxon's test and ANOVA, including factors for treatment group, site and a treatment by site interaction.

Economic Analysis

Results of Literature Review on Economics of Intrathecal Baclofen Infusion

No formal economic analysis of intrathecal baclofen incorporating consideration of benefits was identified from the literature, although a number of cost analyses were identified.

NHS R&D, United Kingdom, 2003

Beard et al.(18) conducted a literature search to identify economic evidence relating to treatments for spasticity in MS. No formal cost-effectiveness analyses were found. Although literature was found on treatment effectiveness, implying potential economic benefits through the improved management of patients, none of these papers attempted to calculate formal cost-effectiveness ratios, estimates of utility or overall treatment costs.(18)

Beard et al. identified 4 studies that closely approximated formal health economic evaluations and dealt with the use of intrathecal baclofen in the treatment of MS related spasticity and its impact on hospitalization rates. These 4 studies are summarized in Table 24.

Two of the studies are Canadian.(5;40). Nance et al.(5) compared the hospital admissions of 6 patients with SCI or MS 2 years prior to intrathecal baclofen and 2 years post-treatment. Two years prior to treatment, there were 376 inpatient hospital days (average 63 days). Two years after treatment, there were 136 inpatient days (average 23 days), none of which were related to spasticity. The authors reported an average net saving in 1995 of CDN $25,250 per patient, taking into account the cost of the pump and hospital days. Nance et al. considered treatment to be cost-effective.

Becker et al.(40) examined the hospital costs of 9 patients 1 year prior and after implantation of an intrathecal pump. Prior to implantation, patients had 755 acute hospital days (average 84 days). After 1 year of implantation, patients had 259 hospital days (average 29 days). Based on the cost of the hospital stay of CDN $570 per day in 1995, reductions in hospital days gave an average saving of CDN $31,000 per patients (excluding the pump and implant).

The studies provided 3 separate estimates of bed days used for patients without or prior to intrathecal baclofen: 19 days, 32 days, and 84 days. Beard et al. suggested that the differences may have been due to differences in patient selection and care settings. Beard et al. assumed an average UK cost per inpatient day of £211, which represents costs of £4,000, £6,800 and £17,700 respectively.

The number of bed days used during the year of implantation ranged from 21 days to 29 days.(18) This corresponds to costs of £4,400-£6,100 for the hospitalization related to the intrathecal baclofen procedure.(18)

Overall, Beard et al. stated that these studies imply the likelihood of significant cost offsets and patient benefits from avoided hospitalizations post-treatment, but they did not attempt to combine this with any form of cost of treatment and overall utility gain per patient.(18)

The cause of spasticity in these studies was not always MS. Causes included cerebral damage and SCI. Therefore, generalization of the results specifically to MS patients may not be valid. The studies included a very small number of patients.

Table 24: Economic studies of intrathecal baclofen From Beard et al.(18)

Study	Patient Characteristics	Method	Results	Savings and Comments
Nance et al. (5) 1995 Canada	6 patients SCI or MS	Comparison of hospital admissions, causally related to spasticity, 2 years prior to treatment, 2 years post-treatment	2 years prior to treatment: 376 inpatient hospital days (range 0-186 days, average 63 days). 2 years after treatment: 136 in patient days (range 11-36 days, average 23 days), none of which was due to spasticity. All admissions post-treatment were related to screening, implantation, treatment of problems related to the intrathecal drug delivery devices and problems related to marked reduction in muscle tone.	Average net savings of CDN $25,250 per patient, taking account of the cost of pump and hospital days (average cost per inpatient day CDN $813). Authors consider treatment to be cost-effective. The number of days used within the post-treatment years may be overestimated owing to use of placebo days in the screening phase. 2/6 patients reported ability to decrease personal attendant services and 1 patient obtained employment following treatment. 2/6 patients had skin ulcers which healed following treatment. (unclear if these 2 patients were the same 2/6 patients who reported ability to decrease personal attendant services).
Postma et al.,(41) 1999 Netherlands	18 patients 11 MS, 7 SCI 15 matched patients of similar age, sex and diagnosis (9 MS, 6 SCI)	Comparison of the number of days in hospital between groups 1 year prior to implantation and 1 year following implantation.	Average number of hospital days in year of implant in treated group was 31.5; 9.9 in the test phase, 12.3 for the implantation phase and 8.4 resulting from complications. Average number of hospital days 18.7 for the matched patients. In the year following implantation, no significant difference was found.	A calculation of the average direct costs that would be likely to occur in a non-experimental situation was made in this study. For this analysis, only 2 days were allocated to the test phase, 10.3 days for the implantation phase, and 8.4 days for complications. If this had been the case, the average number of days for the treated group would have been 20.7, i.e., 2 additional days in comparison to the matched group. For the non-experimental situation, the total average cost of selection, testing, implantation and medical followup amounted to US $28,473 per patient for the first year.
Becker et al.(40), 1995 Canada	9 patients. 6 MS, 2 cervical SCI and 1 head injury	Hospitalization costs 1 year prior and 1 year post-implantation	Prior to implantation: 755 acute hospital days (range 0-319, average 84 days). Year of implantation: 259 days (range 10-48, average 29 days)	Based on cost of hospital stay of CDN $570 per day, reductions in hospital days give average saving of CDN $31,000 per patient (excluding pump and implant). At time of implantation, 6 of the 9 patients were institutionalized in either chronic or acute care hospitals owing to problems managing their spasticity. Following treatment, 3 patients were discharged after prolonged hospitalization, 2 to their own home and 1 to a group home. Savings likely to be underestimated as 2 patients were in chronic care institutions prior to implantation and thus would not have required acute care. The authors concluded intrathecal baclofen to be beneficial in terms of nursing assessment, patient

				satisfaction and cost-effectiveness.
Ordia et al., 1996 USA	10 patients MS or SCI 59 patients in total had pump implant, but only the first 10 were included in the cost study.	Number of bed days used for 1 year prior and 1 year following implantation. Hospitalizations were all cause and not specifically related to spasticity.	Prior to implantation: 95 bed days. Post-implantation: 68 bed days, i.e., 2.7 days per patient saved for general hospitalizations in 1 year. Also 58 days used for screening and implantation, i.e., 5.8 days used per patient for the screening and implantation.	Study does not report the proportion of days that are related to spasticity and thus may include admissions for unrelated causes. Similarly, there is no information as to the number of post implant bed days that are due to complications from the procedure. The number of bed days reported is low as patients who received acute rehabilitation less than 1 year prior to surgery were excluded from cost study. Authors concluded that intrathecal baclofen is cost-effective for treatment of severe intractable spinal spasticity. This was based upon an average cost of US $2,500 per day.

Table reproduced with permission from the NCCHTA; From Beard S, Hunn A, Wight J. Treatments for spasticity and pain in multiple sclerosis: a systematic review. [Review] [154 refs]. Health Technology Assessment (Winchester, England) 2003; 7(40):iii, ix.

■ Sampson et al. (42) reviewed the effectiveness of continuous intrathecal baclofen infusion in terms of improvements in function and QOL and considered the cost effectiveness of the intervention.

The full review of the evidence of effectiveness and cost assumptions was reported in the 2000 Trent Institute for Health Services Research.(3)

Inclusion criteria were the same as previously reported, however, because the authors were also looking at functional benefits, the studies had to allow calculation of the proportion of patients who achieved at least one of the following outcomes:

1. Bedbound patients becoming able to sit in a wheelchair
2. Patients who had severe difficulty sitting in a wheelchair becoming able to sit comfortably
3. Wheelchair users improving their wheelchair mobility
4. Wheelchair users improving their ability to transfer
5. Wheelchair bound patients becoming ambulatory
6. Ambulatory patients improving their ability to walk
7. Improved ability to perform ADL
8. Improved nursing care
9. Patients with skin integrity problems who showed improvements in these symptoms
10. Reduction in spasm-related pain

Studies in which only measurements of patient impairment were recorded, such as the Ashworth score, spasm score or reflex score were not included because these measures provide some indication of the physiologic effect of the intervention, but do not necessarily relate to improvements in function or QoL.

Sampson et al. examined the impact of continuous intrathecal baclofen infusion on the HRQoL of 3 categories of patients with different levels of disability as follows:

Category 1, Bedbound patients experiencing severe spasm related pain
Category 2, Bedbound patients who were not in pain
Category 3, Wheelchair users with moderate spasm-related pain

The categories were chosen to represent a range of patients who may be considered for continuous intrathecal baclofen infusion, “concentrating on the dimensions of mobility and pain, because these are the most likely to be affected.”

Seventeen of the 94 studies identified met the inclusion criteria. Almost all the studies had open followup with no control groups. In general, studies which used controls did so only to examine the effect of test doses of baclofen rather than to assess long-term benefits. A variety of different outcomes were reported, but functional and QOL outcomes were generally not measured using standard scores. Studies often included patients with different causes of spasticity, thereby making it difficult to assess whether the effectiveness of continuous intrathecal baclofen infusion was related to the underlying disease. In none of the identified studies were QOL measures used, nor was cost-effectiveness considered.

In all the included trials, it was specified that patients must have severe disabling spasticity refractory to treatment with oral medications and that they must have shown a response to the bolus dose.

Results of Studies

The studies indicated that approximately two thirds of patients who were bedbound because of their spasticity could be seated in a wheelchair following intrathecal baclofen. Eleven percent of patients who were wheelchair bound became able to walk with assistance. Forty percent of ambulatory patients had some improvement in their ability to walk, however, a small proportion (9%) experienced a deterioration in their ability to walk.(42)

Costs and Cost/Benefit of Continuous Intrathecal Baclofen Infusion - Sampson et al.(42), United Kingdom

The cost of intrathecal baclofen infusion was estimated to be approximately £11,700 ($17,890 US) for the assessment, test dose and implantation procedure with followup costs of £580 to £1,160 ($887-$1,174 US) per annum, based on an average of 4 to 8 refills per annum.

The total discounted cost over a 5-year period is estimated at 15,420 ($23,578 US). The costs per QALY for Category 1, 2 and 3 were £6,900 ($10,550), £12,790 ($19,560), and £8,030 ($12,280) respectively.

Sensitivity Analysis

The initial cost of treatment was estimated at between £10,000 (using the lower cost estimates and assuming a 2 day inpatient stay for the test dose and 5 days for the procedure) and £16,000 (using the higher cost estimates and assuming a 5 day inpatient stay for the test dose and 8 days for the procedure). Assuming an average of 6 refills per annum, this equates to a total discounted cost of between £13,000 and £19,000 for the 5-year period.

Sampson et al. stated that the cost effectiveness of continuous intrathecal baclofen infusion will rise above £20,000 per QALY if the average annual QALY gain is less than approximately 0.15 or if the cost of continuous intrathecal baclofen infusion is above £19,000 ($29,000 US) for the 5-year period.(42)

Conclusion

Sampson et al.(42) concluded:

1. There is sufficient evidence of an acceptable cost/benefit ratio to justify the use of continuous intrathecal baclofen infusion in patients who have not responded to less invasive therapy and are bedbound because of severe spasticity or who are wheelchair bound with severe spasm-related pain.

2. The evidence for use of intrathecal baclofen in other patient groups is limited.

3. Future research should measure functional benefits in different patient groups and collect primary HRQoL data ideally within the context of large, national trials.

Limitations to the study by Sampson et al.(42) included:

- Small number of trials in which functional rather than physiologic benefits of continuous intrathecal baclofen infusion in severe spasticity were measured. However, no previous studies reviewed the functional benefits from treatment or its effect on QoL. Although the cost was considered in some previous studies, there were no previous attempts to value functional benefits in terms of HRQoL to

measure HTQoL directly, or to perform economic analyses. This is due partly to the paucity of studies of functional benefits and partly to difficulties in choosing suitable outcome measures with which to assess HRQoL directly in these patients.

- Estimation of cost/benefit ratio from pooled estimates of benefit in a series of small nonrandomized studies by using assumed HRQoL states. Sampson et al. acknowledged that although this method is imperfect, it is the best available option given the absence of primary HRQoL data and of large, high quality trials in this area in which adequate followup and suitable functional outcome measures were used.
- Results were concentrated on improvements in mobility and pain scores, which could be measured using the EQ-5D. Improvements in other areas such as ambulation, ability to sleep, urinary function, and social functioning may provide significant increases in the QoL for these patients, although generic QoL measures such as the EQ-5D are not sufficiently sensitive to measure all these changes.
- The EQ-5D is based on valuations made by the general population, which may differ from those of the treatment group.
- Direct costs of treatment were assessed. Potential savings that may accrue from reductions in hospitalizations, orthopedic surgery or nursing care were not addressed.

Trent Institute for Health Services Research, United Kingdom, 2000

In addition to the above analysis published in 2002, Sampson et al.(42) (in the Trent Institute for Health Services Research Report) also examined in detail:

- Reductions in hospital stay
- Pressure sores/decubitus ulcers
- Orthopedic surgery
- Reductions in oral treatments or other interventions
- Orthoses and other aids
- Reductions in caregiver resources
- Indirect costs

The costs of intrathecal baclofen arise from the cost of the procedure, followup and support, and costs of potential complications.(3) The initial high cost of intrathecal baclofen therapy comes from screening, the cost of the pump, and the hospitalization required to establish dose requirements.(3) Following initial hospitalization, the costs are reduced considerably.(3) The pumps require a refill every 2-3 months.(3)

The cost of hospitalization reported within the literature varies depending upon whether complications occurred. However, costs of complications should be less significant than those reported in many of the studies due to improvements of the pump itself and physician experience.(3)

The typical length of stay in an acute care facility after an uncomplicated implant has been reported to be between 3 and 10 days.(3) The average length of stay within an inpatient ward in the UKL is considered to be around 5 days.(3)

Screening costs are incurred for all patients who are eligible for intrathecal baclofen, including those who do not respond to the bolus dose. The test dose requires hospitalization of approximately 2 to 3 days. Approximately 70% to 80% of children tested for response to intrathecal baclofen will undergo implantation.

In more recent pumps, battery life may last up to 7 years.(3) Replacing a pump involves a procedure similar to the initial implant.(3) Optimally, the pump is removed without affecting the catheter in which

case the procedure is less lengthy and requires less time in hospital.(3)

Sampson et al stated that whether the need for physiotherapy increases or decreases following intrathecal baclofen infusion is unknown.(3) Albright suggested that the frequency of physical therapy after pump insertion depends on the goal of the treatment; if the goal is to improve gait, therapy is often given 3 times a week.(43) If the aim is to facilitate care, patients may need therapy once a week to maintain range of motion, or not at all.(43)

In the UK, Sampson et al. estimated the cost of administering the test dose, pump implantation and equipment to be between £10,500 and £12,900.(3) Additional annual costs of £580 to £870 were estimated for followup and refill.(3)

The majority of complications usually occur within the first few months following implantation, with further complications potentially arising from inappropriate dose. The potential for error depends upon the experience of the surgeon, cognitive function of patients (related to patient selection) and the caregivers.

Reductions in Hospital Stay

The impact on hospitalization requirements following intrathecal baclofen have been reported for the United States (44), Canada(5;40) and the Netherlands(41). These are discussed below.

The savings reported by Nance et al.(5) and Becker et al.(40), both published in 1995, refer to hospitalization days related to spasticity. Nance et al. reports a 40 day average reduction in the number of bed days used over 2 years, and Becker et al reports a 55 day average reduction in the number of bed days used over one year. The difference in numbers could be due to a greater degree of disability in the population reported by Becker et al. as there were patients suffering skin breakdown who had considerable resource requirements.

The savings reported by Ordia et al.(44) in 1996 do not relate specifically to spasticity and there is no information provided as to the reason for hospitalization prior to or post intrathecal baclofen infusion.

Postma et al.(41) provided a detailed cost analysis of the costs and savings of intrathecal baclofen infusion in the Netherlands. The study showed no significant difference in the number of hospital days used by patients undergoing intrathecal baclofen infusion and the control group in the year following intrathecal baclofen. For the implantation year, there were 18.7 days used on average by the control group compared to an estimated average of 20.7 days related to the intrathecal baclofen procedure, and no further days related to spasticity for the intrathecal baclofen group.

The 3 papers provide estimates of bed days used for patients without or prior to intrathecal baclofen: 19(41), 32 (63 days over 2 years)(5) and 84 days(40). The differences are due to different patient selection and care settings. Assuming an average cost per inpatient day of £211, this represents costs of £4,000, £6,000 and £17,000 respectively.(3)

The number of bed days used during the year of implantation ranges from 21to 29(41);Becker WJ, 1995 118 /id} days. This corresponds to costs of £4,400 to £6,100 for the hospitalization related to the intrathecal baclofen procedure.(3)

Pressure Sores/Decubitus Ulcers

Pressure sores require either long periods of hospitalization or intensive community nursing care. It is

estimated that the total national cost in the UK for the treatment of pressure sores is approximately £755 million a year.(3) A full thickened sacral ulcer extends hospital stay by over 25 weeks at a cost of £26,000 including extra staffing, drugs, dressings and hospital overheads. Costs for pressure ulcers differ depending on the ulcer stage and care setting. Sampson et al. reported that local estimates of costs for treating pressure sores are around £17,000 for a Grade 4 pressure sore and £5,000 for Grade 3.(3)

Orthopedic Surgery

The use of intrathecal baclofen in patients with spasticity due to CP may defer the onset of muscle contractures, hip dislocations and potentially reduce the onset of scoliosis.(3)

The resulting reduction in the need for orthopedic surgery for patients undergoing intrathecal baclofen has been reported by Gerszten et al.(33) and the authors suggested a reduction of 66% in orthopedic operations needed following intrathecal baclofen. However, it is unclear whether the procedures were avoided or delayed.(33) Neither the actual operations avoided, nor the costs associated with these procedures, is documented within the article.

Local UK costing reports the costs of common orthopedic procedures for this CP patient group as follows:

Adductor releases	£2,000
Open or closed adductor tenotomy	£1,500 to £2,000 (excluding to physiotherapy)
Hamstring release	£2,500
Salter's osteotomy or Chiari osteotomy (for hip dislocation)	£5,000

The number of orthopedic procedures avoided can depend upon the age of the child.(3) If the child is treated within the early stages, it is considered likely that orthopedic procedures may be avoided altogether.(3) In an older child (7-10 years), further orthopedic work, e.g., Achilles tendons and hamstring releases may be necessary.(3)

Reductions in Oral Treatments or Other Interventions

No economic analyses are available that look at reductions in oral treatments post-pump implantation.

The cost of the drug for intrathecal baclofen should be offset by reductions in oral treatments, which are prescribed in higher doses.(3)

Orthoses and Other Aids

No economic analyses are available that look at the use of orthoses and other aids post-pump implantation.

Improved management of spasticity may lead to a reduction in seating aids, wheelchairs, spinal jackets (due to scoliosis) and orthoses. A reduction in spasticity was reported to decrease the need for specially designed wheelchairs designed to accommodate extended legs due to spasticity and allow a patient to switch to a less expensive compact model.(45) A compact wheelchair would prevent the need for remodeling of a home hallway and entranceways.

Reductions in Caregiver Resources

Although reductions in the caregiving time required and increased ease of care are frequently reported, there is no quantification of the potential savings which may be realized.(3)

Similarly, savings have been reported in terms of reductions in the need for institutional care(40;41), but the potential scale of the cost reduction is not quantified.

Indirect Costs

Further potential impact on costs may be achieved through indirect costs, as some patients were reported to return to work following intrathecal baclofen, or to further their education due to reductions in spasticity.(5;41) However, these costs have not been quantified within the literature.

Estimation of Cost-effectiveness and/or Cost-Utility

Sampson et al. stated that since there is no quantified measure by which the QALYs gained by the use of intrathecal baclofen can be measured, it is not possible to provide an estimate of the cost per QALY for the treatment. (3) However, by performing threshold sensitivity analyses, an indication of the potential cost-effectiveness can be provided. (3)

Scenario 1: Using Average Costs per Year Over the Period of Treatment

Assuming total costs of £17,600 for 7 years of treatment, i.e. an average cost per year of £2,500 and a benefit of 0.13 QALYs per year (i.e., 0.88 QALYs for the 7-year period), would produce a cost-effectiveness ratio of £20,000.

Assuming total costs of £15,800 for 5 years of treatment, i.e., an average cost per year of £3,200 and a benefit of 0.16 QALYs per year (i.e., 0.9 QALYs for the 7 year period) would produce a cost-effectiveness ratio of £20,000.

Scenario 2: Discounting Costs and Benefits to Account for Different Costs in Each Year

Assuming a cost of £11,870 in year one and 870 in following years, and discounting both costs and benefits at 6%, the number of QALYs gained over the 7 year period would be 0.83 to produce a cost-effectiveness ration of £20,000, i.e., 0.14 QALYs for year one.

Assuming the pump lasts for 5 years and discounting costs and benefits at 6%, the number of QALYs gained over the period would have go be 0.77 to produce a cost-effectiveness ratio of £20,000, i.e., 0.17 QALYs in year 1.

Sensitivity of Cost per QALY Assumption to QALY Gains and Treatment Costs

Table 25 presents the number of QALYs that the treatment would need to provide per annum to achieve different levels of cost-effectiveness, based upon variance in the initial cost of the treatment and discounting costs and benefits at 6% per annum. As the cost of the pump and the inpatient stay for implantation are the largest cost elements, variance in the initial cost will have the greatest effect upon cost-effectiveness. The impact of altering the cost of refill/followup, depending upon the number of refills per year, is significantly lower.

Table 25: Annual gains in health state values (QALY gains) required per year of treatment for different cost-utility ratios and initial treatment costs - Costs and benefits discounted at 6% per year over a 5-year period From Sampson et al.(3)

	Initial Cost of Treatment			
Cost per QALY ratio	**£10,000**	**£12,000**	**£14,000**	**£16,000**
£5,000	0.58	0.67	0.76	0.85
£10,000	0.29	0.34	0.38	0.43
£15,000	0.19	0.22	0.25	0.28
£20,000	0.15	0.17	0.19	0.21
£25,000	0.12	0.13	0.15	0.17

Table reprinted with permission; From Sampson FC, Hayward A, Evans G, Touch S, Morton R, Vloeburghs M et al. The effectiveness of intrathecal baclofen in the management of patients with severe spasticity. 2000. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield. Guidance Note for Purchasers: 00/01

The potential savings due to reduced resource requirements for the management of spasticity were detailed by Sampson et al. (Table 26).(3)

Table 26: Summary table of potential savings From Sampson et al.(3)

Reduction	Avoidance	Potential Savings
Hospitalization (MS & SCI)	20 days' hospitalization	£4,220
	55 days' hospitalization	£11,605
Orthopedic surgery (CP)	1 adductor release	£2,000
	1 open or closed tenotomy	£1,500
	1 hamstring release	£2,500
	Hip dislocation	£5,000
Pressure sore (MS & SCI)	50% chance of avoiding pressure sore – using cost of pressure sore of £26,000	£13,000
	50% chance of avoiding pressure sore – using cost of pressure sore of £17,000	£8,500

Table reprinted with permission; From Sampson FC, Hayward A, Evans G, Touch S, Morton R, Vloeburghs M et al. The effectiveness of intrathecal baclofen in the management of patients with severe spasticity. 2000. Sheffield: Trent Institute for Health Services Research, Universities of Leicester, Nottingham and Sheffield. Guidance Note for Purchasers: 00/01

Summary of Economic Analysis by Sampson et al.

- Cost of intrathecal baclofen is estimated to be approximately £11,700 for the initial assessment, test procedure, implantation procedure and equipment. In addition, there will be further costs of around £870 per annum for refill and followup.
- Battery life may be up to 7 years, although life expectancy may be less than this period for some patients, notably MS patients.
- No studies report on QoL utilities for intrathecal baclofen.
- Assuming 5 years of benefit are obtained from the pump implantation, an average annual QoL utility gain of around 0.16 would result in a cost-utility ratio of £20,000.
- Clinical opinion and Index of Health Related Quality of Life measures analysis suggested this scale of QoL improvement to be possible.
- Although there is a lack of data in the literature, the high initial cost of intrathecal baclofen implantation could be offset by reductions in pressure sores, other admissions related to spasticity, orthopedic procedures and reductions in requirements for orthoses or other aids.

Cost Analysis of Intrathecal Baclofen Compared to Selective Functional Posterior Rhizotomy (SFPR) – British Columbia (1995)

In 1995, Steinbok et al.(46) analyzed the relative cost of SFPR and continuous intrathecal baclofen in the treatment of children with severe spastic quadriplegia related to CP at British Columbia's Children's Hospital. No attempt was made to analyze the efficacy of the two treatments.

Nine children received intrathecal baclofen. All of these patients were severely affected, intellectually delayed, spastic quadriplegic children who were mobilized in a special wheelchair pushed by an attendant. Some of these patients were considered inappropriate candidates for SFPR.

Of a total of 100 children who had undergone SFPR from 1988 onward, 10 patients with the most severe spastic quadriplegia related to CP were chosen to match the 9 patients in the baclofen group as closely as possible with respect to the severity and extent of the spastic quadriplegia and intellectual delay. The selected SFPR patients were all spastic quadriplegic, intellectually delayed and mobilized in a wheelchair operated by an attendant, but were generally not as severely affected, particularly with respect to upper limb function, as were the patients in the baclofen group.

The hospital records of these patients were reviewed and a clinical care flow chart was created to identify the various points of contact with members of the health care team so that cost points could be identified and costs calculated.

Since baclofen was provided free as part of a research protocol, and the real cost of the drug was not known, the cost assigned for the baclofen was only the drug preparation fee charged by the pharmacy department.

Costs were determined for a followup period of 1 year after the initial intervention for all health care that was related to the SFPR procedure or to the continuous intrathecal baclofen therapy.

Initial baclofen screening consisted of insertion of a lumbar subarachnoid catheter attached to an implanted access port and repeated injections of baclofen via the access port were carried out to determine the efficacy of the drug. If the response to baclofen was satisfactory, the patient was readmitted to surgery where the access device was removed and replaced with a continuous infusion pump.

Patients

The age range in the baclofen group was 6.0-17.5 years with a mean of 11.8 years. The age range in the SFPR group was 6.0-16.1 years with a mean of 10.4 years. The patients in the baclofen group who had a pump implanted were followed from 13 to 54 months (mean 36 months) and patients who received rhizotomy were followed from 17 to 43 months (mean 27 months).

Of the 9 patients in the intrathecal baclofen group, 3 did not respond favourably to baclofen during screening and did not have a pump inserted.

In the first postoperative year, 2 of the 6 patients with pumps required surgery for complications associated with the baclofen treatment. One child had 4 further operations: 1 for effusion around the pump; 1 for extrusion of the lumbar catheter from the subarachnoid space; and 2 for CSF fistula repair. In the other child, 1 further procedure was performed for a pump effusion. In addition, 2 patients were hospitalized for adjustment of the baclofen dose when there was deterioration in the relief of spasticity or

symptoms suggestive of overdose.

In the first postoperative year, no patient in the rhizotomy group was re-hospitalized for problems associated with rhizotomy.

The total cost for the 6 successful implants was CDN $326,197.86. When one takes into account the cost of CDN $58,780.71 incurred by the 3 patients who were screened but did not have a pump implanted, the cost to the healthcare system per successful pump implant averaged CDN $64,163.10 in the first year after implantation of the pump. The majority of the costs (72%) were related to hospitalization, which occurred at a number of stages during the course of management.

All 10 patients underwent rhizotomy and the total cost for the 10 patients was CDN $169,135.40 with an average cost per patient of CDN $16,913.54. Hospital costs accounted for 65% of the total costs.

Comparison of Baclofen and SFPR Costs

For both intrathecal baclofen and SFPR, the major costs incurred had to do with hospitalization. The higher total average cost per patient treated with baclofen compared to SFPR was related to a more prolonged hospital stay associated with preoperative assessment, screening for suitability for pump insertion and management of complications. Paramedical costs were higher in the SFPR group because of intensive postoperative physiotherapy.

Major limitations to the study by Steinbok et al. (46) included:

- Cost analysis was based on the experience at British Columbia's Children's Hospital starting from 1988 and therefore the results may not be current or generalizable to other institutions or to other patient populations.
- Efficacy of the 2 treatments was not investigated.
- The two treatment arms were not comparable. The authors acknowledged that there were more severely affected children in the baclofen arm.
- The number of children who received intrathecal baclofen was less than the number of patients who had rhizotomies. The high incidence of complications with intrathecal baclofen may indicate a learning curve, and that with more experience with intrathecal baclofen the complication rate may decrease.
- Use of an implanted port to screen patients. Alternative ways to screen patients include a lumbar puncture or externalized lumbar subarachnoid catheter.
- Intrathecal baclofen was experimental during the time of the study and was provided free to the pharmacy. The authors stated that at the time of the publication, intrathecal baclofen cost CDN $136 per 10 mg vial.
- Part of the cost associated with both the use of intrathecal baclofen and selective rhizotomy was related to experimental protocols and for both types of treatments, patient were in funded research studies.

Ontario-Based Economic Analysis

Disclaimer: This economic analysis represents an estimate only, based on assumptions and costing methodologies that have been explicitly stated. These estimates will change if different assumptions and costing methodologies are applied for the purpose of developing implementation plans for the technology.

Hospitalization Costs

In fiscal year (FY) 2003, 12 hospital separations were identified from the discharge abstracts database that could have been associated with intrathecal baclofen pump insertion (a combination of ICD-10 CA diagnosis codes and ICD-10 CA CCI procedure codes were used.) In fiscal year (FY) 2002, 7 hospital separations were identified. Given the small number of cases, cases in both fiscal years were used to determine the cost per case. The prospectively adjusted-for-complexity resource intensity weights (PAC-10 weights) were used to determine a dollar value of each hospital separations based on a weight of 1.0 having a dollar value of $4,505 during FY 2003 and $4,539 in FY 2002 (Personal Communication, May 2005). The mean PAC-10 weight in FY 2003 was 1.97, and 1.80[1] in FY 2002, with an associated cost of $8,113 per hospital separation in FY 2003 and $8,923 per hospital separation in FY 2002. The overall average for both fiscal years was $8,625 per hospital separation with an average length of stay of 5.5 days.

There is also a short hospitalization involving a lumbar puncture (average 2.5 day length of stay) prior to the insertion of the pump to determine suitability for pump insertion. Between 70% - 80% of patients who undergo this procedure are eventually fitted with a pump (Personal Communication, May 10, 2005). The PAC-10 weight for these hospital separations averages approximately 0.5, with an average length-of-stay of 2.5 days. The associated cost is approximately $2,250 per hospital separation in which patients are screened for suitability.

The total cost for hospitalizations is approximately $10,875, and based on the current volume of approximately 10 procedures per year, the total provincial cost of hospitalizations related to intrathecal pump insertion is approximately $108,750.

Device Costs

The cost of the pump is approximately $11,500 including the cost of refills for the first year (figure provided by local Ontario hospital). As a result, the current annual device costs based on current volumes of approximately 10 procedures per year would be in the range of $115,000. The pump generally lasts from 5 – 7 years, at which point it must be replaced.

Professional (Ontario Health Insurance Program) Costs

Professional Costs per Treated Patient: (Source: MOHLTC Provider Services Branch)

$102 = pre-screening costs (includes 0.5 hour neurosurgeon time & outpatient clinic)
$55 = test dose (including lumbar puncture, lumbar catheter, procedure)
$936 = surgery for pump insertion
$204 = four refills per year performed by neurosurgeon

$1,300 = total OHIP costs per treated patient

[1]One hospital separation with a PAC-10 weight ≈ 40 was removed from the sample upon which the average PAC-10 was calculated in FY 2002.

Total OHIP costs, based on a current volume of approximately 10 procedures per year, would be over $13,000 annually.[2]

Total Costs:

The total expected costs per treated patient in the first year are approximately $24,000, excluding the costs associated with pathology, radiology, and microbiology. Based on approximately 10 procedures per year, the total cost to the province of using this technology at current levels is approximately $240,000 annually.

Downstream Cost Savings:

Based on reduced need for hospitalizations and medications for spasticity and its sequellae, we estimate that the total savings to the system due to intrathecal baclofen pump insertion would be at least $5,000 per case per year. Assuming remaining life expectancy of at least 30 years, the total cost savings to the system could total $150,000 over a person's lifetime or approximately $77,000, discounted to the present at a 5% annual rate as suggested by the Canadian Coordinating Office on Health Technology Assessment (CCOHTA.)

Diffusion:

Based on an estimated prevalence of spasticity appropriate for the pump of 1,500-2,400, there is a potential backlog for procedures in this range. Based on the rate of pump insertion in the United States, we estimate that if Ontario were to adopt similar utilization levels for this technology there would be approximately 300 pump insertions per year at an annual cost of $8.2 -$8.4 million, until the backlog was eliminated.

[2] Since a greater number of people undergo the lumbar puncture than go through with the entire protocol (approximately 20-30% more people), the total costs will exceed the per-patient treated costs by a factor of slightly greater than 10--the current annual volume.

Existing Guidelines for Use of Technology

National Institute for Clinical Excellence (NICE), United Kingdom 2003

Multiple Sclerosis: Management of Multiple Sclerosis in Primary and Secondary Care

The following grading scheme was used by NICE (Table 27).

Table 27: Grading scheme used by NICE

Recommendation Grade	Evidence
A	Directly based on category 1 evidence
B	Directly based on: ➢ Category 2 evidence, or ➢ Extrapolated recommendation from category 1 evidence
C	Directly based on: ➢ Category 3 evidence, or ➢ Extrapolated recommendation from category 1 or 2 evidence
D	Directly based on: ➢ Category 4 evidence, or ➢ Extrapolated recommendation from category 1, 2, or 3 evidence
DS	Evidence from diagnostic studies
HSC	Health Service Circular 2002/2004
Evidence Category	**Source**
1a	Evidence from meta-analysis of RCTs
1b	Evidence from at least one RCT
2a	Evidence from at least one controlled study without randomization
2b	Evidence from at least one other type of quasiexperimental study
3	Evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies and case-control studies
4	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities

From: Multiple Sclerosis: Management of Multiple Sclerosis in Primary and Secondary Care; Clinical Guideline 8, November 2003; National Institute for Clinical Excellence

Spasticity and Spasms

- Each professional in contact with a person with MS who has any muscle weakness should consider whether spasticity or spasms are a significant problem, or a contributing factor to the person's current clinical state. (GRADE D)
- If spasticity or spasms are present, then simple causative or aggravating factors such as pain and infection should be sought and treated. (GRADE D)
- Every person with MS who has persistent spasticity and/or spasms should be seen by a neurophysiotherapist to assess and advise on physical techniques, such as passive stretching and other physical techniques to reduce spasticity and especially to avoid the development of contractures. Families and carers should be taught how to prevent problem deterioration, and a monitoring system should be put in place. (GRADE D)
- More active specific measures should be considered only if the spasms or spasticity are causing pain or distress, or are limiting (further) the individual's dependence and activities. In this case, both benefits and risks should be considered carefully. A specific goal (or goals) should be set, but will

rarely include improved performance in activities. (GRADE D)

- Initial specific pharmacological treatment for bothersome regional or global spasticity or spasms should be with baclofen or gabapentin. (GRADE A)
    - The following should be given only if treatment with baclofen or gabapentin is unsuccessful or side effects are intolerable:
        - Tizanidine (GRADE A)
        - Diazepam (GRADE D)
        - Clonazepam (GRADE D)
        - Dantrolene (GRADE D)
    - Combinations of medicines and other medicines such as anticonvulsants should only be used after seeking further specialist advice (GRADE D)
- People with MS who have troublesome spasticity and spasms unresponsive to simpler treatments, should be seen by a team specializing in the assessment and management of spasticity. (GRADE D)
    - The team should consider using one or more of the following:
        - Standing and weight bearing through legs (GRADE D)
        - Splints (GRADE D)
        - Serial casting (GRADE C)
        - Special or customized seating, such as tilt in space chairs (GRADE D)
        - Intrathecal baclofen (GRADE A)
        - Phenol injections to motor points or intrathecally (GRADE D)
- Intramuscular botulinum toxin should not be used routinely, but can be considered for relatively localized hypertonia or spasticity that is not responding to other treatments. It should be used when specific goals can be identified, (GRADE B) and:
    - In the context of a specialist service that can consider all aspects of rehabilitation (e.g., seating) (GRADE B)
    - By someone with appropriate experience and expertise (GRADE B)
    - Followed by active input from a neurophysiotherapist (GRADE B)

Aetna, United States (November 30, 2004)

Implantable Infusion Pumps

Aetna considers implanted infusion pumps medically necessary durable medical equipment when all of the following criteria are met:

- The drug is medically necessary for the treatment of members; and
- It is medically necessary that the drug be administered by an implanted infusion pump; and
- The infusion pump has been approved by the FDA for infusion of the particular drug that is to be administered.

Anti-spasmodic drugs

Aetna considers an implantable infusion pump medically necessary when used to intrathecally administer anti-spasmodic drugs (e.g., baclofen) to treat chronic intractable spasticity in persons who have proven unresponsive to less invasive medical therapy as determined by the following criteria:

A. Member has failed a six-week trial of non-invasive methods of spasticity control, such as oral anti-spasmodic drugs, either because these methods fail to adequately control the spasticity or produce intolerable side effects; *and*

B. Member has a favorable response to a trial intrathecal dosage of the anti-spasmodic drug prior to pump implantation.

Intrathecal baclofen (Lioresal) is considered medically necessary for the treatment of intractable spasticity caused by spinal cord disease, spinal cord injury, or multiple sclerosis. Baclofen is considered medically necessary for persons who require spasticity to sustain upright posture, balance in locomotion, or increased function.

Documentation in the member's medical record should indicate that the member's spasticity was unresponsive to other treatment methods and that the oral form of baclofen was ineffective in controlling spasticity or that the member could not tolerate the oral form of the drug.

The medical record should document that the member showed a favorable response to the trial dosage of the baclofen before subsequent dosages are considered medically necessary. An implanted pump for continuous fusion is considered not medically necessary for members who do not respond to a 100 mcg intrathecal bolus.

Members must be monitored closely in a fully equipped and staffed environment during the screening phase and dosage-titration period immediately following the implant.

Contraindications to implantable infusion pumps

Implantable infusion pumps are considered *not* medically necessary for persons with the following contraindications to implantable infusion pumps:

1. Members with known allergy or hypersensitivity to the drug being used (e.g., oral baclofen, morphine, etc.); *or*
2. Members who have an active infection that may increase the risk of the implantable infusion pump; *or*
3. Members whose body size is insufficient to support the weight and bulk of the device; *or*
4. Members with other implanted programmable devices where the crosstalk between devices may inadvertently change the prescription.

Blue Cross Blue Shield of North Carolina, United States, May 2003

Implantable Infusion Pumps

Implantable infusion pumps are considered eligible for coverage by prior authorization when used to deliver drugs having FDA approval for this route of access and for the related indication.

Severe Spasticity

Implantable infusion pumps may be medically necessary for baclofen infusion in patients with severe spasticity of spinal cord origin or cerebral origin in patients who are unresponsive to or who cannot tolerate oral baclofen therapy.

Conclusion

- Level 2 evidence of the effectiveness of intrathecal baclofen infusion for the short-term reduction of severe spasticity in patients who are unresponsive or cannot tolerate oral baclofen
- Level 3 evidence of the effectiveness of intrathecal baclofen for the long-term reduction of severe spasticity in patients who are unresponsive or cannot tolerate oral baclofen
- Level 4 qualitative evidence of functional improvement for patients who are unresponsive or cannot tolerate oral baclofen
- Intrathecal baclofen is cost-effective with costs which may or may not be avoided in the Ontario health system
- True functional use remains to be determined

Appraisal/Policy Development

Policy Considerations/Implications

Patient Outcomes

Spasticity
Quality of life
Transfers
Bedridden patients sitting in wheelchair
Improved ability to sit comfortably
Improved wheelchair mobility
Decreased need for personal attendant services
Improved ease of nursing care
Skin integrity

Sleeping urinary function

Dosage Creep

- Creedon et al.(13) reported that it was in the immediate post-implantation period, that the most accelerated dose increases occurred. Drug holidays are one method used to interrupt dose escalation, but they may be temporarily successful.
- Longer-term followup is necessary to determine if these individuals ultimately require de-implantation due to progressive drug tolerance or if the tolerance and dosing increases eventually level off.

Demographics

Table 28: Estimated prevalence and incidence of SCI, CP and MS from the literature

Condition	Incidence per 100,000 per year	Prevalence per 100,000
SCI	1.7	72
CP	2.6	50
MS	3-7	100-200

Stakeholders

Less caregiving required by:

- Nursing staff in long term care facilities
- Families of affected patients

Physicians

- Neurosurgeons
- Anesthetists
- General surgeon

System pressures

Potential changes in:
Longterm care stay
Hospital stay
Patient transfer
Reduction in management of pressure sores
Reduction in pain
Orthopedic surgery

- Avoidance of adductor release, tenotomy, hamstring release and hip dislocation

Reduction in oral baclofen
Use of orthoses and other aids or adaptations
Care resources

- Improved sleep may lead to reductions in night care
- Improved ability to eat alone
- Patients may be seated and dress more easily
- Reduction in number of carers required to assist one person

Glossary

Baclofen: A drug designed to impede the release of excitatory neurotransmitters.

Contracture: A condition of fixed high resistance to passive stretch of a muscle, resulting from fibrosis of the tissues supporting the muscles or the joints or from disorders of the muscle fibres.

Contracture deformity: Deformity of a limb without discernable primary changes of bone.

Diplegic: Paralysis affecting either both arms or both legs

Dorsal: Relating to the back.

Dorsal rhizotomy: A neurosurgical procedure designed to reduce spasticity in individuals with cerebral palsy. The surgery requires testing individual sensory nerve rootlets to determine those rootlets that when stimulated, produce abnormal electrophysiologic responses. Rootlets producing abnormal responses are cut and normal responding rootlets are spared.

Hemiplegia: Paralysis affecting the limbs on only one side of the body.

Intrathecal: Injection of a substance through the theca of the spinal cord into the subarachnoid space.

Muscle release: Surgical technique that involves cutting tendons or muscle to increase muscle length.

Quadriplegia: Paralysis affecting all 4 limbs.

Serial Casting: Treatment consisting of a series of casts that are put on a part of the body to reduce tightness and/or increase the amount of joint movement in patients who have trouble extending their arms or legs. The limb is stretched, cast, and after 5-10 days, the cast is removed. The limb is then stretched again and a new cast is applied. This continues until the joint is stretched as far as possible.

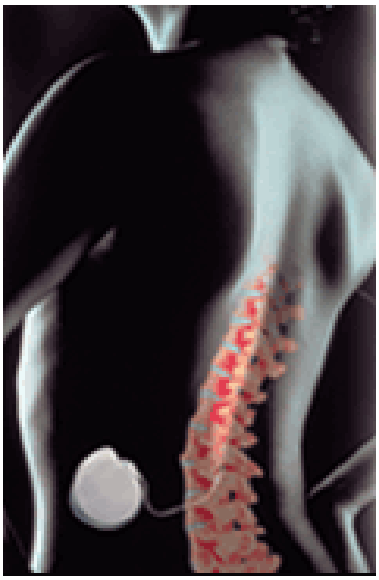
Spasticity: A motor disorder characterized by increased muscle tone with heightened deep tendon reflexes.

Tendon release: Sectioning of tendon to treat contracture by lengthening the muscle-tendon unit.

Ventral: Located on or near the lower front of the body; the abdominal area.

Appendices

Appendix 1. Intrathecal Pump.



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