INTRATHECAL BACLOFEN EVIDENCE COMPENDIUM

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INTRODUCTION

INTRATHECAL BACLOFEN THERAPY℠

APPROVED FOR THE TREATMENT OF SEVERE SPASTICITY OF CEREBRAL OR SPINAL ORIGIN

Severe spasticity of spinal or cerebral origin is challenging to control effectively. Spasticity can result from spinal cord injury (SCI), multiple sclerosis (MS), cerebral palsy (CP), brain injury (BI), or stroke. The mainstays of treatment include traditional rehabilitation therapy, oral pharmacologic treatments, injection therapy, and destructive neurosurgical procedures. Many patients reject these treatments because they provide insufficient relief, cause intolerable side effects, or because of reluctance to undergo a permanent procedure.

Oral baclofen (USP) for example, is an antispasmodic drug that acts primarily at the spinal level. For some patients, the amount of drug that penetrates the blood-brain barrier does not provide adequate relief for their severe spasticity. Increasing the dose often leads to a high concentration of drug in the plasma and results in unacceptable central nervous system (CNS) effects such as sedation, dizziness, and muscle weakness.[53,56,61,64]

Intrathecal baclofen therapy (ITB Therapy℠) is delivered by the Medtronic SynchroMed® Drug Infusion System, which consists of an implantable, programmable pump and an intrathecal catheter. Lioresal® Intrathecal (baclofen injection) is administered directly to the intrathecal space surrounding the spinal cord. This allows effective drug concentrations to reach the cerebrospinal fluid (CSF), while the plasma remains relatively unaffected, compared with oral administration.[63,65]

ITB therapy is indicated for use in the management of severe spasticity. Patients with severe spasticity of spinal origin are appropriate candidates for ITB therapy when they experience unacceptable CNS side effects at effective oral doses of oral baclofen, or when their spasticity does not respond adequately to oral baclofen. Patients with severe spasticity resulting from traumatic brain injury should wait at least one year after the injury before consideration of ITB therapy.[a]

Patients should first respond to a screening dose of intrathecal baclofen through a single-bolus dose delivered via spinal catheter or lumbar puncture. If the screening test is positive, the patient may be appropriate for long-term therapy. ITB therapy can be titrated to individual patient needs and its effects are reversible by explant of the pump.

This compendium presents the clinical and economic value of ITB therapy for the treatment of severe spasticity. It summarizes historical clinical trials that supported regulatory approval, and describes efficacy, safety, and cost-analysis data from peer-reviewed scientific literature. The evidence demonstrates the safety profile and efficacy of ITB therapy for severe spasticity of spinal and cerebral origin. Studies show that ITB therapy can effectively control severe spasticity in the long term. Numerous reports also show improvement in patients' activities of daily living. Refer to Important Safety information by clicking on the icon at the top right.

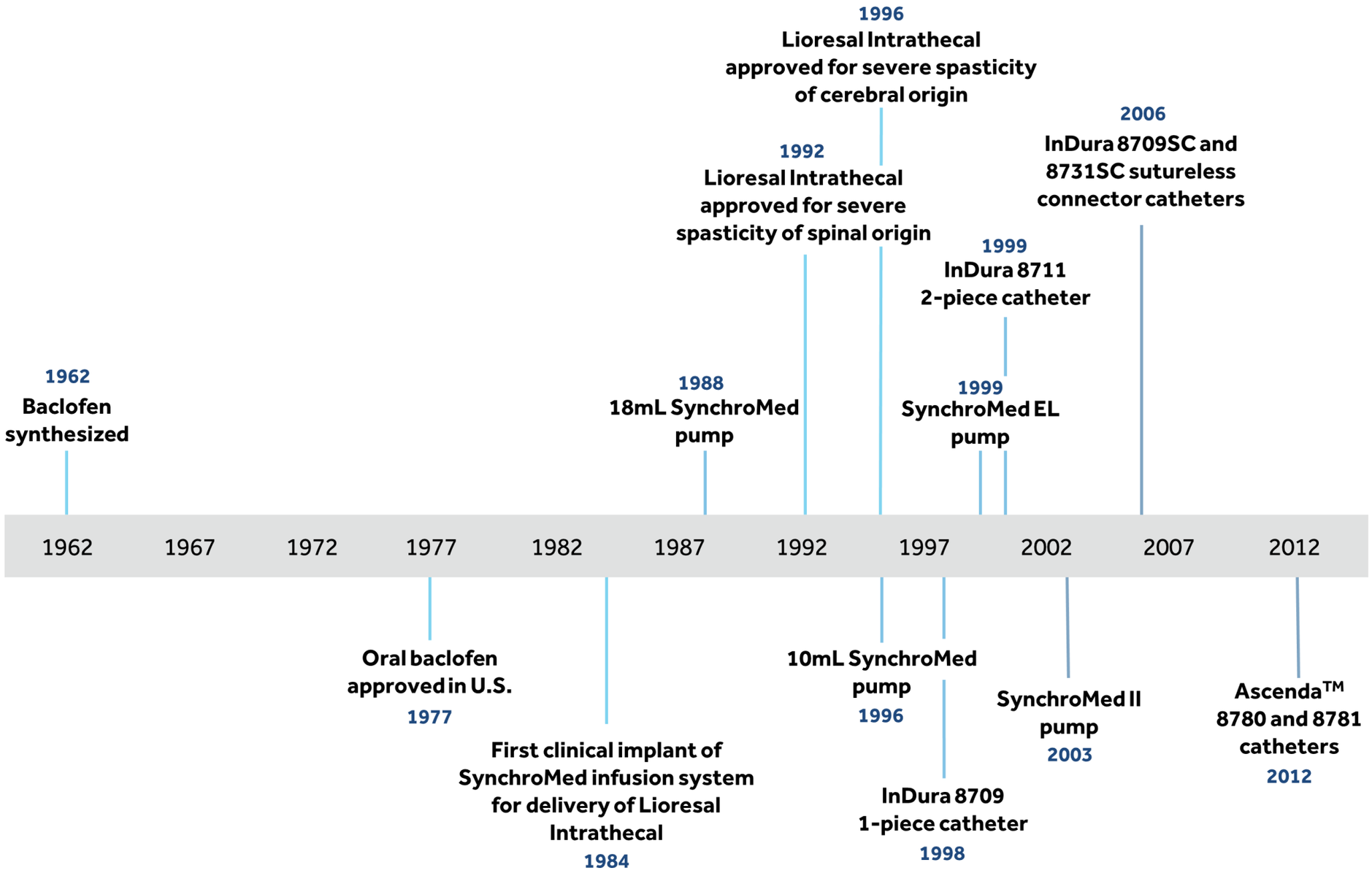
The compendium is not intended to be an exhaustive or systematic review, but rather focuses on the most relevant literature in terms of outcomes data, regardless of positive or negative results. Older studies or those with a very small sample size may not be represented in the summary in favor of more current studies reporting on more extensive outcomes measures.

[a] *In clinical trials, the safety and efficacy of ITB therapy for traumatic brain injury was not studied for patients less than 1 year post injury.*

Acronyms: Brain Injury (BI); Central Nervous System (CNS); Cerebral Palsy (CP); Cerebrospinal Fluid (CSF); Gross Motor Function Classification System (GMFCS); Intrathecal Baclofen (ITB); Multiple Sclerosis (MS); Spinal Cord Injury (SCI).

HISTORICAL MILESTONES IN THE U.S.

ITB therapy has been commercially available in the U.S. since 1992 for severe spasticity of spinal origin, and since 1996 for severe spasticity of cerebral origin.



CLINICAL DATA SUPPORTING U.S. REGULATORY APPROVAL

SPINAL ORIGIN SPASTICITY

Two controlled clinical investigations demonstrated the efficacy and safety of ITB therapy for severe spasticity due to MS or SCI, and served as the basis for U.S. FDA approval of ITB therapy for severe spinal origin spasticity in 1992.

The studies compared the effects of a single intrathecal dose of 3-day infusion of ITB to placebo. ITB provided a significant and consistent improvement in spasticity compared to placebo in both studies.

Penn et al conducted a double-blind randomized crossover study of ITB in 20 adult patients with severe spasticity due to MS or SCI from 1986 to 1988. Ten patients with each etiology were enrolled. Each patient received up to 3 bolus doses of Lioresal Intrathecal (baclofen injection) (50, 75, and 100 micrograms) in an open-label screening test. All patients responded, and were enrolled in a randomized, placebo-controlled, crossover trial in which the treatment periods consisted of 3 days of continuous delivery of Lioresal Intrathecal vs. placebo delivered by the SynchroMed pump. Analyses of Lioresal Intrathecal vs. placebo demonstrated a statistically significant difference between the treatment groups. There were no significant differences between the groups with regard to age, gender, and duration of spasticity. Lioresal Intrathecal was effective regardless of the patient's disease (MS or SCI) or the continuation of oral baclofen. The results of this screening trial and a subsequent open-label long-term follow-up extension (conducted under the same IND) were published in 1989 and 1992.[8,9]

Based on the encouraging results of the study by Penn et al, in 1988 Medtronic initiated a multi-center, double-blind, randomized clinical trial to evaluate ITB versus placebo in 45 adult patients with severe spasticity due to MS or SCI. Patients were randomized to receive a bolus dose of 50 micrograms of Lioresal Intrathecal and placebo in random order. Those who did not respond were re-randomized to receive 75 micrograms of Lioresal Intrathecal and placebo in random order, and those who did not respond to this dose received 100 micrograms of Lioresal Intrathecal and placebo in random order. The group treated with Lioresal Intrathecal showed a statistically significant decrease in spasticity and frequency of spasms. Disease status (MS or SCI) and continuation of oral baclofen did not affect the results. The results of this randomized double-blind screening trial and a subsequent open-label long term follow-up extension were published in 1993.[3]

Supportive evidence of the efficacy of ITB therapy was demonstrated in 3 studies: a U.S. double-blind, placebo controlled, randomized screening trial[2]; an open-label long-term safety and efficacy study conducted in Europe[6] ; and a U.S. double-blind placebo-controlled screening trial with an open-label long-term extension.[5]

Labeled safety data consists of pooled data from 576 prospectively-followed patients who received Lioresal Intrathecal via the SynchroMed Pump for periods of one day (screening test) to eight years (long-term infusion) from 1984 through 1992. Because of the open, uncontrolled nature of the patient data, a causal linkage between the observed events and the administration of Lioresal Intrathecal could not be reliably assessed in many cases, and many of the reported adverse events are known to occur in association with the underlying conditions being treated. Many of the more commonly reported reactions such as hypotonia, somnolence, dizziness, paresthesia, vomiting, convulsions, and headache appear clearly drug related. Consult the Lioresal Intrathecal prescribing information for a complete listing of adverse events.

Acronyms: Investigational New Drug (IND); Multiple Sclerosis (MS); Spinal Cord Injury (SCI).

CLINICAL DATA SUPPORTING U.S. REGULATORY APPROVAL

CEREBRAL ORIGIN SPASTICITY

Three randomized controlled clinical investigations demonstrated the efficacy and safety of ITB therapy for the management of severe spasticity due to CP, BI, or stroke, and served as the basis for U.S. FDA approval of an expanded indication in 1996.

There is no safety/efficacy data in children under 4 years of age, or for patients less than 1 year post-traumatic brain injury. ITB provided a significant reduction in spasticity compared to placebo when delivered by a single intrathecal bolus, and spasticity improvement was maintained with long-term ITB infusion in the open-label phases.

In 1987 Albright et al initiated a single-center study of ITB in 82 pediatric and adult patients with severe spasticity primarily due to CP. Response to baclofen injection was evaluated in a double-blind, placebo-controlled crossover screening phase. There was a clinically and statistically significant response to ITB vs. placebo. An open-label follow-up phase with 53 implanted patients demonstrated that efficacy was maintained with long-term infusion. Outcomes that included some of the patients in this study were published in 1991 and 1993.[1,2]

Medtronic initiated a multi-center study in 1992 to confirm Dr. Albright's findings. The study enrolled 51 pediatric and adult patients with severe spasticity due to CP. The study design and clinical outcomes were similar to the Albright study. The results of this study were published in 2000.[4]

Meythaler et al conducted a multi-center cross-over study of 11 adult patients with BI at least one year post-injury. Patients were randomized to receive a bolus dose of 50 micrograms of Lioresal Intrathecal and placebo in random order. There was a clinically and statistically significant response to ITB vs. placebo. This study had a small sample size and did not provide data that could be reliably analyzed. Despite the small sample size, the study yielded a nearly significant test statistic ($P = 0.066$) and provided directionally favorable results. The results of this study were published in 1996.[7]

Supportive evidence of the long-term efficacy of ITB therapy was demonstrated in 4 physician-sponsored uncontrolled studies.[6] The studies enrolled a total of 16 patients with severe spasticity of cerebral origin (primarily CP) who received long-term infusion. The patient population and study design were generally similar to the controlled studies, consisting of a screening phase and a long-term follow-up infusion phase.

Labeled safety data: The safety profile of ITB in patients with spasticity of cerebral origin was not significantly different from the adverse events reported for patients with spasticity of spinal origin. A total of 211 patients in pre-marketing controlled and open-label studies contributed to the labeled safety data. Patients received Lioresal Intrathecal for one day (screening test) to seven years (long-term infusion) from 1988 to 1996. Consult the Lioresal Intrathecal prescribing information for a complete listing of adverse events.

Acronyms: Brain Injury (BI); Cerebral Palsy (CP); Food and Drug Administration (FDA).

CONSENSUS STATEMENTS AND PRACTICE GUIDELINES

Consensus statements and practice guidelines aid in the safe and effective delivery of ITB therapy in children, adolescents, and adults. Safety and effectiveness have not been established for children younger than 4 years of age, or for patients less than 1 year post-traumatic brain injury.

Saulino M, Ivanhoe CB, McGuire JR, Ridley B, Shilt JS, Boster AL. Best Practices for Intrathecal Baclofen Therapy: Patient Selection. *Neuromodulation*. 2016;19(6):607-615.[19]

Summary:

Consensus statement on **patient selection for ITB therapy** from a 2013 ITB Therapy Best Practices Panel.

Key Conclusions:

The panel emphasized the importance of timing of intervention; clinicians should weigh the risks and benefits of intervention with the understanding that ITB is not a last-resort therapy. Spasticity treatment is not linear. ITB therapy is an option within an integrated, interdisciplinary treatment plan. It should be considered for patients with problematic generalized spasticity.

Boster AL, Bennett SE, Bilsky GS, Gudesblatt M, Koelbel SF, McManus M, Saulino M. Best Practices for Intrathecal Baclofen Therapy: Screening Test. *Neuromodulation*. 2016;19(6):616-622.[13]

Summary:

Consensus statement on **best clinical practices for the ITB screening test** from a 2013 ITB Therapy Best Practices Panel.

Key Conclusions:

ITB screening tests are a best practice, and are conducted to evaluate clinical response and goal achievement. Therapy goals should be predetermined, individualized, and realistic; taking into consideration active and passive function. A successful trial achieves the predetermined goals.

Boster AL, Adair RL, Gooch JL, Nelson ME, Toomer A, Urquidez J, Saulino M. Best Practices for Intrathecal Baclofen Therapy: Dosing and Long-Term Management. *Neuromodulation*. 2016;19(6):623-631.[12]

Summary:

Consensus statement on **best clinical practices for long-term ITB dosing and patient management** from a 2013 ITB Therapy Best Practices Panel.

Key Conclusions:

At therapy initiation, the goal is to titrate the dose as quickly and as safely as possible. At each follow-up visit, conduct subjective, objective, and goal achievement assessments. The optimal ITB dose depends on several factors including the patient's predetermined therapy goals. Patients may benefit from a variety of dosing options such as simple continuous, day/night mode, and periodic bolus mode.

Saulino M, Anderson DJ, Doble J, Farid R, Gul F, Konrad P, Boster AL. Best Practices for Intrathecal Baclofen Therapy: Troubleshooting. *Neuromodulation*. 2016;19(6):632-641.[18]

Summary:

Consensus statement on **pump and catheter diagnostic evaluation and ITB therapy adverse event management** from a 2013 ITB Therapy Best Practices Panel.

Key Conclusions:

An evaluation process should be started when a patient is receiving suboptimal therapy. The panel provided recommendations for diagnostic evaluation, system investigation, drug investigation, and treatment of infection, ITB overdose, and ITB underdose/withdrawal. It is best practice to develop a structured, consistent on-call system for patients to guide emergency department physicians through ITB emergency protocols. Patients should be educated on the signs and symptoms of ITB overdose and withdrawal.

Dressler D, Berweck S, Chatzikalfas A, et al. Intrathecal Baclofen therapy in Germany: Proceedings of the IAB-Interdisciplinary Working Group for Movement Disorders Consensus Meeting. *J Neural Transm.* 2015;122(11):1573-1579.[15]

Summary:

Proceedings from a 2013 Interdisciplinary Working Group for Movement Disorders (IAB) in Germany, focused on **ITB therapy indications, screening, complications, and interdisciplinary framework.**

Key Conclusions:

As echoed in prior guidelines, this consensus panel stresses the need for an interdisciplinary care team to treat spasticity and manage ITB therapy. Response to ITB dose adjustments in the titration phase should reference predefined therapy goals. The authors provide an algorithm of several spasticity treatment methods. ITB therapy has a role in the treatment of severe, refractory spasticity.

Berweck S, Lutjen S, Voss W, et al. Use of intrathecal baclofen in children and adolescents: interdisciplinary consensus table 2013. *Neuropediatrics.* 2014;45(5):294-308.[11]

Summary:

Consensus statement on **ITB therapy for children and adolescents with movement disorders** from a 2013 ITB Working Group in Germany.

Key Conclusions:

A comprehensive, integrative treatment approach delivered by a multidisciplinary team is imperative to the use of ITB as a treatment for spasticity in children and adolescents. Regular check-ups should review progress toward predefined treatment goals and use of aids and orthoses.

Dan B, Motta F, Vles JS, et al. Consensus on the appropriate use of intrathecal baclofen (ITB) therapy in paediatric spasticity. *Eur J Paediatr Neurol.* 2010;14(1):19-28.[14]

Summary:

Consensus statement on **ITB therapy for pediatric patients with spasticity** from a 2008 European Working Group for Spasticity in Children.

Key Conclusions:

Treatment goals for ITB therapy are highly dependent on gross motor abilities (GMFCS). This guideline emphasizes the importance of goal-setting for the pediatric patient and the caregiver based on their abilities. The working group's spasticity treatment pathway categorizes patients according to GMFCS level (I-III and IV-V).

Francisco GE, Yablon SA, Schiess MC, Wiggs L, Cavalier S, Grissom S. Consensus panel guidelines for the use of intrathecal baclofen therapy in poststroke spastic hypertonia. *Top Stroke Rehabil.* 2006;13(4):74-85.[16]

Summary:

Consensus statement on **ITB therapy for post-stroke spasticity** from a 2005 ITB Stroke Consensus Panel.

Key Conclusions:

Appropriate candidates are motivated patients with post-stroke spasticity who have not responded adequately to, or could not tolerate, other treatments. Experts recommend individualized treatment goals that take into consideration the patient's level of functioning and ambulatory status. Goal setting for higher-functioning and ambulatory patients must account for a wide range of functional tasks and change in active motor function.

Acronyms: Gross Motor Function Classification System (GMFCS).

Albright AL, Turner M, Pattisapu JV. Best-practice surgical techniques for intrathecal baclofen therapy. *J Neurosurg*. 2006;104(4 Suppl):233-239.[10]

Summary:

Consensus statement on **pump and catheter surgical technique** from a 2004 ITB Therapy Best Practices Forum.

Key Conclusions:

Surgical implant techniques can minimize risks for CSF leakage and surgery-related infection. Guidance is provided for managing surgery-related complications such as CSF leaks and accumulations, and pump and catheter-related infections. Neurosurgeons are the recommended implanters in pediatric cases, and should be actively involved in patient selection and the evaluation and management of complications.

Ridley B, Rawlins PK. Intrathecal baclofen therapy: ten steps toward best practice. *J Neurosci Nurs*. 2006;38(2):72-82.[17]

Summary:

Consensus statement on **ITB therapy patient management** from a 2004 ITB Therapy Best Practices Forum.

Key Conclusions:

The guidelines emphasize the importance of an integrated care team, careful patient selection, clearly defined and documented treatment goals, and ongoing evaluation to facilitate optimal therapy outcomes.

Medtronic provided funding support for some of the above working groups.

Acronyms: Cerebrospinal Fluid (CSF).

IMPORTANT SAFETY INFORMATION

Surgical complications are possible and include infection, meningitis, spinal fluid leak, paralysis, and headache.

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 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 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.

The most frequent drug adverse events associated with ITB therapy vary by indication but include: hypotonia (34.7%), somnolence (20.9%), headache (10.7%), convulsion (10.0%), dizziness (8.0%), urinary retention (8.0%), nausea (7.3%) and paresthesia (6.7%). Adverse events related to device and implant procedures are catheter dislodgement from the intrathecal space, catheter break/cut, and implant site infection including meningitis. Electromagnetic interference (EMI) and magnetic resonance imaging (MRI) may cause patient injury, system damage, operational changes to the pump, and changes in flow rate. Pump system component failures leading to pump stall, or dosing/programming errors may result in clinically significant overdose or underdose. Acute massive overdose may result in coma and may be life-threatening.

This therapy is contraindicated in patients who are hypersensitive to baclofen. Infusion system implant is contraindicated if the patient is of insufficient body size, requires a pump implant deeper than 2.5 cm, or, in the presence of spinal anomalies or active infection.

Access the full Lioresal Intrathecal prescribing information here.

SPASTICITY

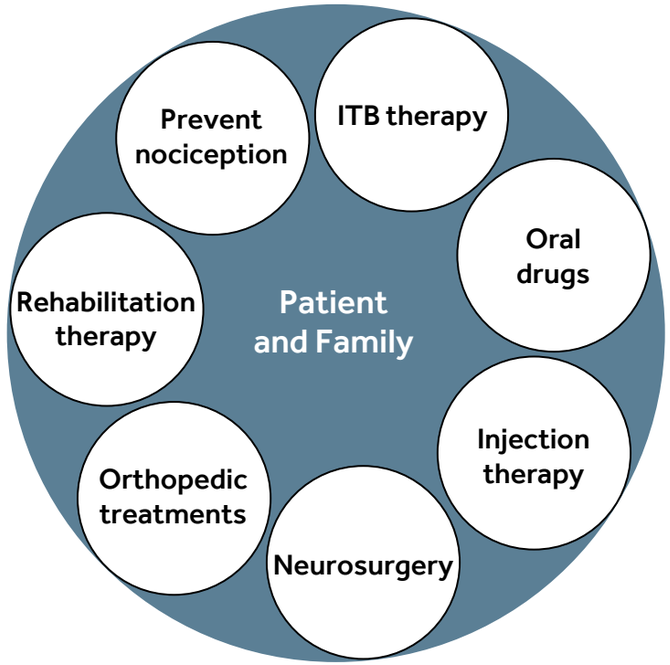
DEFINITION

Upper motor neuron damage disturbs the normal pattern of supraspinal excitatory and inhibitory neurons that regulate muscles. Spasticity is caused by a decrease in descending inhibitory signals from the brain, resulting in an abnormal increase in muscle tone. Thus, spasticity is defined in pathophysiology terms as "disordered sensory-motor control, resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles."[36] This definition identifies that abnormal muscle activity is caused by an upper motor neuron lesion.

Spasticity can also be defined as how spastic muscle responds to imposed movement. Spasticity is defined clinically as "hypertonia in which 1 or both of the following signs are present: 1) resistance to externally imposed movement increases with increasing speed of stretch and varies with the direction of joint movement, and/or 2) resistance to externally imposed movement rises rapidly above a threshold speed or joint angle".[39] This definition addresses that muscles are more sensitive and resistant to stretch in spasticity. The velocity-dependent resistance found in spasticity distinguishes it from other forms of abnormal muscle tension such as dystonia and rigidity. Active movement, not just passive stretch, is affected by spasticity. When an agonist muscle is voluntary contracted and its antagonist muscle is stretched, a spastic stretch reflex can be triggered in the antagonist muscle.[31]

Spasticity may not always be disabling or problematic. However, voluntary movements such as transferring from a bed to a wheelchair, walking, and other activities of daily living can be impacted by spasticity. Disabling or problematic spasticity can cause functional limitations that impact self-care and the ability of caregivers to provide care. Disabling spasticity may impact clinical/body function (permanent muscle contracture, weakness, pain, limited range of motion and mobility), individual activities and functioning (difficulty performing personal hygiene, difficulty sitting and transferring), and community participation and quality of life (impaired communication, decreased social interaction and recreation).[26,30]

There are multidisciplinary options for spasticity management. Treatment plans may take into consideration the severity and distribution of spasticity, the impact of spasticity on the patient's function and quality of life, the patient's treatment goals, and tolerance for potential adverse effects of treatment options. ITB therapy for the management of severe spasticity is one component of a spectrum of care, and it can generally be implemented in conjunction with other components.

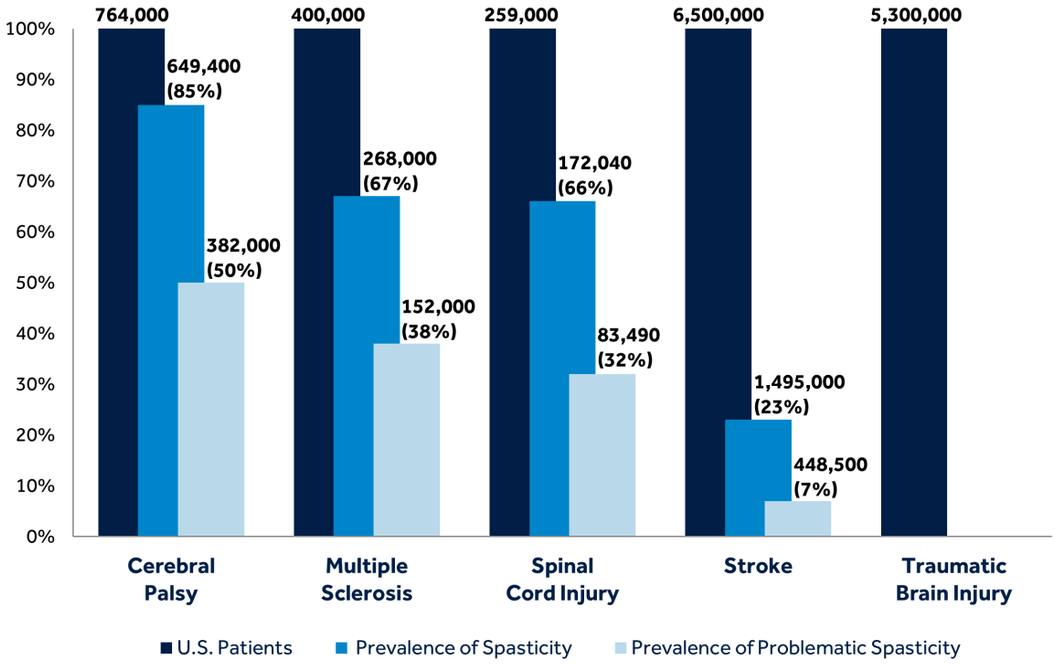


SPECTRUM OF CARE FOR MANAGEMENT OF SPASTICITY

PREVALENCE

Few studies focus solely on the etiologies, prevalence, and incidence of spasticity. Data interpretation is made difficult by the lack of consistent definitions, reliable measures, and the resulting heterogeneity of population registries. An estimate of spasticity prevalence in the U.S., published in 2016 and shown in the table below, was calculated as an average percent from population-based studies.[33] There was insufficient data to determine the prevalence of spasticity in traumatic brain injury. Population-based study data used in the 2016 estimate, as well as data published after this time point, is described in more detail below.

ESTIMATED PREVALENCE OF SPASTICITY IN THE U.S. (2016)[33]



POPULATION-BASED STUDIES

MULTIPLE SCLEROSIS

Several patient survey-based studies in Spain, the U.K., and the U.S. have found that 65-84% of patients with MS experience spasticity.[21,24,35,38] 17-29% of patients in these studies reported severe spasticity.[23,35]

SPINAL CORD INJURY

The incidence and prevalence of SCI differs between developing and developed countries.[40] Spasticity was reported in 40-68% of patients with SCI in U.S., Canadian, and Swedish studies.[28,32,34,41] Patients with cervical injuries were more likely to experience spasticity than patients with thoracic or lumbosacral level injuries.[28,41] Nearly 30% of patients with SCI may experience problematic spasticity.[27,28,32,41]

STROKE

Several clinical studies in England, Sweden, and Germany observed that 20-25% of post-stroke patients develop spasticity.[29,42-45] Most found that spasticity was more frequent in the upper limbs than the lower limbs, and all found that upper limb spasticity was more severe than the lower limbs. One study reported that 4% of patients had disabling spasticity one year post-injury that required intervention such as physiotherapy, orthosis, or pharmacological treatment.[29]

BRAIN INJURY

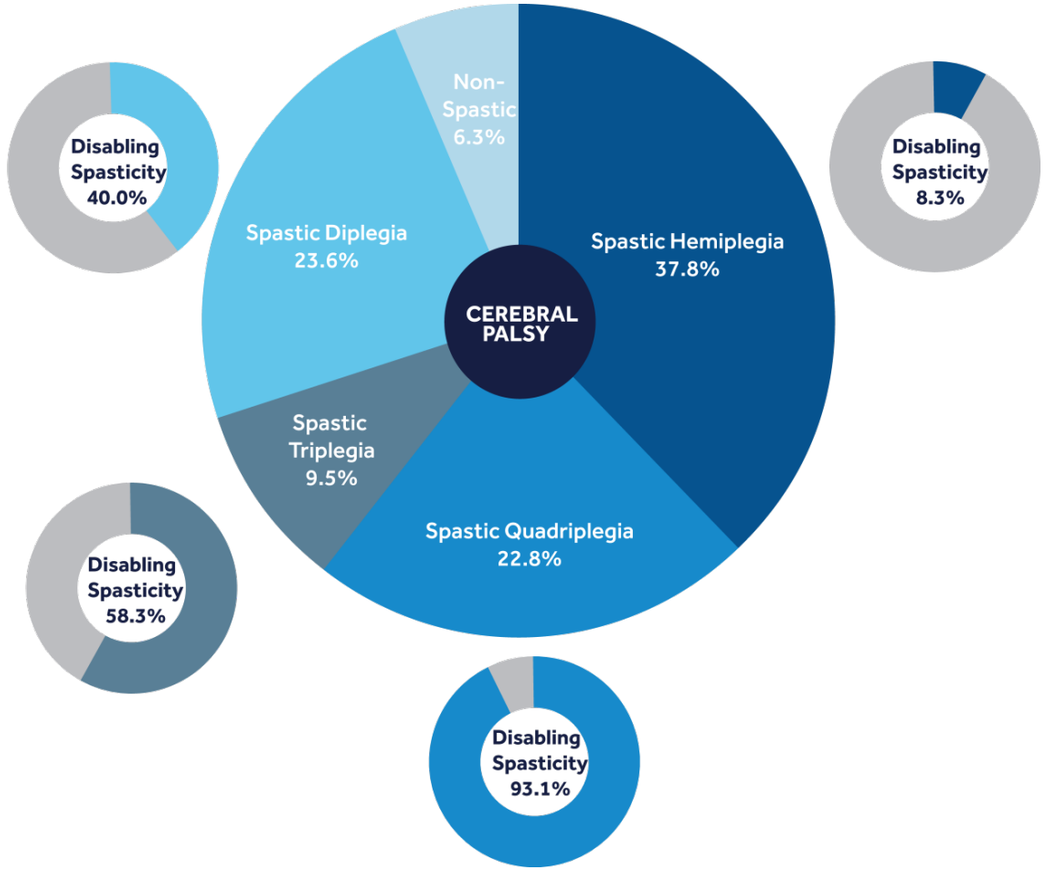
The incidence and prevalence of spasticity in brain injury have not been well characterized. It is estimated that 5% of all TBI are classified as severe, with contractures due to spasticity occurring in up to 85% of patients with severe TBI.[22]

Acronyms: Brain Injury (BI); Multiple Sclerosis (MS); Spinal Cord Injury (SCI); Traumatic Brain Injury (TBI).

CEREBRAL PALSY

Cerebral palsy is the most common cause of spasticity in children and young adults.[20,25] Reid et al compared 28 CP registry studies from eight geographic regions, and found that on average, approximately 90% of patients with CP have a spastic motor type.[37] The range of spastic CP proportion was high (65%-98%) with large heterogeneity, likely due to differences in mixed motor type classification.[37]

Wichers et al conducted a population-based study of the prevalence of CP in Dutch children born between 1977-1988.[46] The authors reported the percentage of patients with severe motor disability* as classified by CP motor subtype, shown below.

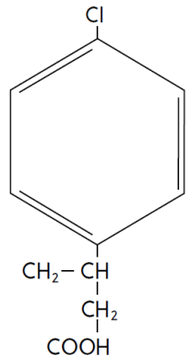


** Disability was defined as severe if the child had not reached a form of independent walking by 5 years of age. Note that 6.3% of children with CP experienced no spasticity.*

Acronyms: Cerebral Palsy (CP).

BACLOFEN PHARMACOLOGY

Baclofen (4 chloro-phenyl-Ɣ-aminobutyric acid), a gamma-aminobutyric acid (GABA) agonist, acts at the spinal cord level to impede the release of excitatory neurotransmitters, such as glutamate and aspartate, that cause spasticity due to hyperexcitability of the stretch reflex.[47]



Baclofen chemical structure

Due to its low lipid solubility, orally administered baclofen crosses the blood-brain barrier poorly and reaches low CSF concentrations.[52,58,65] Thus, systemic doses required to effectively reduce spasticity may result in cerebral nervous system side effects such as sedation, muscular weakness, dizziness, and respiratory depression.[53,56,61,64,69]

Lioresal® Intrathecal (baclofen injection) administration allows higher baclofen concentration to reach the spinal site of action, with resultant plasma concentrations 100 times less than oral administration.[63,65] During ITB therapy, baclofen is infused directly into the intrathecal space where it mixes with CSF. Baclofen binds to GABA-β receptors in the dorsal horn and dorsal root ganglion, stimulating a cascade of second messengers that ultimately hyperpolarize the presynaptic membrane at clinical doses and the postsynaptic membrane at substantially higher doses. This effect inhibits action potential activation and resultant neurotransmitter release within the motor neuron pathways.[50,51,55,57,62,66,72,73] Interruption of the spinal reflex (sensory peripheral afferent input and spinal motor afferent output) produces an antispastic effect by reducing peripheral motor tone.[55]

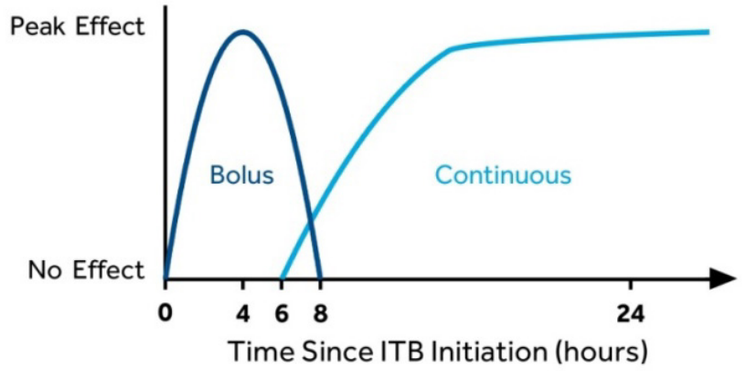
PHARMACODYNAMICS

INTRATHECAL BOLUS

In adults, the onset of action is generally 30 minutes to 1 hour after an intrathecal lumbar bolus injection. Peak spasmolytic effect is seen within approximately 4 hours after dosing and effects may last 4 to 8 hours.[55] Onset, peak response, and duration of action will vary with individual patients depending on the dose and severity of symptoms. The onset, peak response and duration of action is similar in pediatric and adult patients.[63]

CONTINUOUS INFUSION

Continuous ITB is infused by an FDA-approved pump at a much slower rate than an intrathecal bolus. Initial antispastic action is seen at 6 to 8 hours of initiation of continuous infusion. Maximum activity is observed in 24 to 48 hours.[55] No additional information is available for pediatric patients.[63]



Acronyms: Cerebrospinal Fluid (CSF); Gamma-Aminobutyric Acid (GABA).

PHARMACODYNAMIC STUDIES

The majority of clinical pharmacodynamic studies employed a bolus delivery mode. Response to ITB was typically evaluated using the Ashworth/Modified Ashworth spasticity severity scales or the Penn Spasm Frequency Scale.

Study	Cause	Delivery mode	N	Dose (mcg)	Measure	Latency of onset (hours)	Maximum effect (hours)	Duration of effect (hours)
Penn and Kroin 1984[67]	SCI	Bolus	2	5-50	MAS	<1	1-7	6-8
Muller et al 1988[65]	Various	Bolus	30	50-500	MAS/PSFS	1	1-12	8-48
		Continuous	25	Various	MAS/PSFS	6-8	12-24	-
Zierski et al 1988[74]	Various	Bolus	44	10-300	MAS/PSFS	1-2	-	4-24
Albright et al 1991[2]	CP	Bolus	23	25-100	MAS	<2	4	>8
	Various	Bolus	6	25	MAS	<2	4	>8
				50	MAS	<2	8	>8
				100	MAS	<2	4	>8
Sallerin-Caute et al 1991[70]	Various	Bolus	4	75-136	MAS	1	-	9-16
Meythaler et al 1996[7]	TBI	Bolus	11	50	MAS	<1	4	6
Meythaler et al 2001[105]	Stroke	Bolus	22	50	MAS	<1	6	>6
					PSFS	<1	4	>6
					RS	<1	6	>6
Scheinberg et al 2001[71]	CP	Bolus	1	50	MAS	2	4	6
			1	50	MAS	1	4	8
Pohl et al 2003[68]	CP	Bolus	13	100	MAS/ fiberglass cast	0.5-1	3.5-4.5	2-8.5
Heetla et al 2016[54]	Various	Bolus	12	25-100	MAS	1	2-4	8-12

Adapted from Heetla et al (2014)[55]

Bolus dosing patterns during an ITB screening test may produce greater and faster drug distribution within the CSF because the injection volume (approximately 0.5 mL) is delivered over 1 to 2 minutes versus 24 hours during continuous infusion. Increasing kinetic energy with the screening test bolus dose facilitates drug distribution within the intrathecal space and may produce a pharmacodynamic effect that is different than that seen during continuous infusion with an implantable pump.

Compared to simple or variable continuous (constant) administration, periodic bolus dosing via the implantable pump may produce different clinical outcomes.[59,114] To date, there have been no clinical studies that formally evaluate periodic bolus drug administration and subsequent CSF distribution.

Acronyms: Cerebral Palsy (CP); Cerebrospinal Fluid (CSF); Modified Ashworth Scale (MAS); Multiple Sclerosis (MS); Penn Spasm Frequency Scale (PSFS); Reflex Scale (RS); Spinal Cord Injury (SCI); Traumatic Brain Injury (TBI).

PHARMACOKINETICS

There are limited baclofen CSF pharmacokinetic data due to sampling difficulty accessing the CSF space. Some studies avoided spinal tap by withdrawing CSF samples from the infusion system catheter access port. However, this sampling method is fraught with error because it disturbs CSF mixing at the catheter tip. Studies employing spinal tap sampling methods suggest that a lumbar-cisternal concentration gradient of about 4:1 is established along the neuraxis during ITB infusion. This is based upon simultaneous CSF sampling via cisternal and lumbar tap in five patients receiving continuous ITB infusion at the lumbar level, at doses associated with therapeutic efficacy. There was wide variation between subjects. [60] A more recent study delivered ITB through one intrathecal catheter and sampled CSF through a second catheter.[54]

Overall, studies indicate that drug distribution within the spinal CSF is limited and not homogenous, even with increasing infusion rates during continuous drug delivery. The highest intrathecal drug concentrations are typically found at the catheter tip site, and diffuse with a steep concentration gradient.

METABOLISM

The CSF clearance of Lioresal Intrathecal (baclofen injection) calculated from intrathecal bolus or continuous infusion studies approximates CSF turnover. This suggests elimination is by bulk-flow removal of CSF versus metabolism or reabsorption into the vascular space.[63] The mean CSF clearance for Lioresal Intrathecal was approximately 30 mL/hour in a study involving ten patients receiving continuous intrathecal infusion.[63] After a bolus lumbar injection of 50 or 100 mcg Lioresal Intrathecal (n=7), the average CSF elimination half-life was 1.51 hours, CSF clearance was approximately 30 mL/hour.[63] These data indicate that ITB clearance is not affected by infusion mode (bolus versus continuous infusion).

PHARMACOKINETIC STUDIES

Several studies have reported pharmacokinetic data of intrathecal baclofen administration in humans. Varying ITB doses and CSF sampling locations were used. Several of these studies report ITB half-life ranging from 1 to 5 hours.

Study	Delivery mode	N	Dose (mcg)	Vd (mL)	CL (mL/h)	T½ (min)	Css (ng/mL)	Delivery (spinal level)	Sampling (spinal level)
Müller et al 1988[65]	Continuous	8	50 - 1200 / day	-	-	-	130-950	Pump*	-
	Bolus	3	200 - 600	-	-	270†	-	-	-
Sallerin-Caute et al 1991[70]	Bolus	4	75 - 140	119	36	54 - 300	-	T6-T11	T10-L3
Kroin and Penn 1991[60]	Bolus	2	50	85	35	101	-	T12-L2	T12-L2
	Bolus	5	100	86	41	82	-	T12-L2	T12-L2
	Continuous	10	96 - 600 / day	-	29.9	-	76 - 1240	Pump*	Side port*
Albright et al 2007[49]	Continuous	43	70 - 1395 / day	-	-	-	20 - 20,000	Pump*	Side port*
Heetla et al 2016[54]	Bolus	12	25-100	116	55	-	-	T10	T12

Table adapted from Heetla et al (2014)[55]

V_d, volume of distribution; CL, clearance; $T_{½}$, half-life; Css, lumbar steady state concentration

**delivery and sampling through the pump, catheter tip level unknown*

†calculated from graph

Acronyms: Cerebrospinal Fluid (CSF).

PLASMA CONCENTRATION

The majority of Lioresal® Intrathecal (baclofen injection) is cleared through the lymphatic system (CSF turnover) versus being metabolized or reabsorbed into the vascular system. The net result is a very low or undetectable plasma baclofen concentration during ITB therapy.

Concurrent plasma concentrations of baclofen during intrathecal administration are expected to be low (0-5 ng/mL) and are 100 times less than those occurring with oral administration. There are two small case studies involving 6 and 14 patients in whom a single baclofen concentration was determined in plasma at one time point following continuous intrathecal baclofen administration

- Albright and Shultz (1999) report the plasma baclofen concentrations in six children (8 to 18 years old) undergoing continuous ITB infusion for treatment of cerebral spasticity.[48] Plasma levels were at or below 10 ng/mL, the limit of quantitation of the gas chromatography assay, with ITB doses of 77-400 mcg/day. The time of measurement was more than 36 hours after the last dose adjustment.
- Müller et al (1988) discuss the pharmacokinetics of ITB in 14 patients receiving a continuous intrathecal infusion of 50-1200 mcg/day.[65] Plasma baclofen levels (at time points more than 24 hours after start of infusion) ranged from 0-5 ng/mL. The analytical methodology used fluorimetry in combination with thin-layer chromatography.

DOSING IN RENAL AND HEPATIC IMPAIRMENT

Precaution in special patient population: Because Lioresal Intrathecal (baclofen injection) is primarily excreted unchanged by the kidneys, it should be given with caution in patients with impaired renal function and it may be necessary to reduce the dosage.[63]

There are no ITB dosing studies in patients with impaired renal or hepatic function. Careful patient monitoring is essential when administering ITB therapy in patients with renal or hepatic failure.

COST ANALYSIS

Note: Evidence from the literature in this section is presented to assist in formulary decision making. It is not intended for use by healthcare providers to make treatment decisions for individual patients.

Studies between 1995 and 2015 have reported on the cost effectiveness of ITB therapy in patients with severe spasticity across multiple indications. These studies determined and compared healthcare costs for ITB therapy and other management techniques using fee schedules and currencies that do not equate to 2015 US dollars. However, they are illustrative of the costs of ITB therapy over time. While the initial financial outlay for ITB therapy appears to be high, there is evidence that ITB therapy substantially decreases healthcare resource use over time, and can become cost effective.

All cost-effectiveness and cost-utility studies reported that ITB therapy demonstrated appropriate cost-effectiveness in the associated healthcare system. Four cost-effectiveness analyses (three in Europe, one in the United States) demonstrated that ITB therapy provides incremental health benefits at an acceptable incremental cost compared to conventional medical management (CMM) when used to treat disabling spasticity in appropriately selected patients.[78,81,86,92] A fifth analysis (France) showed that ITB therapy provides more health benefits at a lower cost than CMM.[77] Independent health technology assessments conclude that ITB therapy is a cost-saving and cost-effective treatment option for disabling spasticity.[75,80,87,89]

Below is a summary of cost analysis publications looking at incremental cost-effectiveness, quality adjusted life years (QALYs) and willingness-to-pay (WTP) thresholds, and costs associated with ITB therapy. Summaries are organized in order of most recent publication activity.

Vidal J, Slof J, Serrano D et al. Cost-effectiveness of intrathecal baclofen therapy in severe refractory non-focal disabling spasticity: a Spanish hospital perspective. *Expert Rev Pharmacoecon Outcomes Res.* 2016 May (epub ahead of print).[92]

A Markov model estimated long-term clinical and economic outcomes with ITB therapy and CMM for severe refractory non-focal disabling spasticity. Clinical and cost inputs were obtained through a non-interventional, prospective, observational study in a Spanish neurorehabilitation hospital.

Cost Analysis and Key Conclusions:

The analysis suggests that ITB therapy, compared to CMM, increases remaining lifetime costs by €35,605, leads to a QALY gain of 1.06, and an estimated ICER of €33,619 per QALY gained. An ICER close to €30,000 per QALY gained is typically considered an acceptable level for willingness to pay for public funding in Spain. The ICER drops below this threshold when more current clinical practice is considered. Sensitivity analysis results suggest ways to optimize the current clinical pathway in order to reduce procedure costs and improve the ICER. For example, the post- pump implant length of stay is an area to improve by setting targets for clinical and cost-appropriate inpatient stays.

Saulino M, Guillemette S, Leier J, Hinnenthal J. Medical cost impact of intrathecal baclofen therapy for severe spasticity. *Neuromodulation*. 2015;18(2):141-149.[88]

A retrospective claims analysis and actuarial cost model evaluated the effects of ITB therapy on health services utilization and cost of care before and after implant. Health services utilization and associated costs were determined by examining claims data for 409 patients with severe spasticity 3 years pre and postimplant. A CMM comparator was constructed using the patient as his/her own control and followed over time. The model projects over a 30-year time horizon to capture the long-term financial impact of ITB therapy and pump replacements.

Cost Analysis and Key Conclusions:

Despite high initial costs, ITB therapy was less expensive than CMM over the lifetime. The break-even point occurred between 2- to 3 years postimplant. ITB therapy saved $8,009 per patient per year relative to CMM. Savings were derived from reduced inpatient admissions, physician office visits, and ambulatory surgical events. Per-patient costs associated with treating a catheter complication were $2,307, a blended rate of inpatient, outpatient, and physician services. The results of this study suggest that patients receiving ITB therapy would expect to experience a reduction in cumulative future medical costs relative to anticipated costs without ITB therapy.

Acronyms: Conventional Medical Management (CMM); Incremental Cost-Effectiveness Ratio (ICER); Quality-Adjusted Life Year (QALY); Willingness-To-Pay (WTP).

Thrasher TA, Fisher S. Societal costs of intrathecal drug delivery systems--an administrative analysis based on patient claims. *Neuromodulation.* 2013;16(3):261-265.[91]

A retrospective longitudinal analysis evaluated medical and pharmacy claims for 38,951 adult patients between January 2004 and March 2010. Patients receiving intrathecal drug delivery were divided into 3 cohorts according to their conditions: pain (n=23,721), spasticity (n=973), or pain and spasticity (n=14,257). Claims data was provided by 14 commercial health plans in the United States. Costs were inflation-adjusted to 2011 U.S. dollars.

Cost Analysis and Key Conclusions:

Annualized costs were highly variable for patients receiving intrathecal drug delivery, due to the broad spectrum of disease severity and ancillary treatment needs. The mean annualized postimplant societal cost of care ranged from $12,233 (spasticity cohort) to $20,049 (pain plus spasticity cohort). The distribution of costs was skewed in the positive direction in all cohorts. Nearly two-thirds of all societal costs of care were due to inpatient encounters. A small number of patients represented high numbers of medical encounters and associated costs.

Hattori N, Hirayama T, Katayama Y. Cost-effectiveness analysis of intrathecal baclofen therapy in Japan. *Neurol Med Chir.* 2012;52(7):482-487.[79]

A prospective cost-utility analysis evaluated direct and indirect medical costs of 6 patients with severe spasticity who were treated with ITB therapy (SCI n=1, TBI n=2, stroke n=1, other n=2). This study is the first cost-utility analysis for ITB therapy in Japan. The analysis was conducted in a single center, and was adjusted based on medical costs in Japan in 2009.

Cost Analysis and Key Conclusions:

The mean cost of ITB therapy 5 years postimplant was ¥1,554,428 per QALY, well below the ¥6,000,000 per QALY willingness-to-pay threshold. Although limited by a small number of patients, the study shows that ITB therapy in Japan is an acceptable treatment for severe spasticity from a medical-economic perspective.

Bensmail D, Ward AB, Wissel J et al. Cost-effectiveness modeling of intrathecal baclofen therapy versus other interventions for disabling spasticity. *Neurorehabil Neural Repair.* 2009;23(6):546-552.[77]

Modeling and Monte Carlo simulations were used to assess the cost-effectiveness of ITB therapy compared to CMM for patients with severe spasticity. Comprehensive decision trees were constructed to simulate strategies for managing severe spasticity using CMM or ITB therapy as a first-line strategy. Parameters used in each event tree included success rate and medical costs over 2 years. Both treatment and cost components of the analysis were conducted in the context of medical practice in France.

Cost Analysis and Key Conclusions:

The analysis suggested that including ITB therapy as a first-line option resulted in a higher success rate (78.7% vs. 59.3%, P<0.001). ITB therapy had a lower cost (€59,391 vs. €88,272, P<0.001) and overall more favorable cost-effectiveness ratio compared to CMM alone.

Hoving MA, Evers SM, Ament AJ, van Raak EP, Vles JS. Intrathecal baclofen therapy in children with intractable spastic cerebral palsy: a cost-effectiveness analysis. *Dev Med Child Neurol.* 2008;50(6):450-455.[81]

The Dutch national study evaluated cost-effectiveness of ITB therapy for 15 children with CP; ITB in addition to CMM versus CMM alone over a 12-month period. Costs in the preimplant year, during which participants received only CMM, were compared to costs in the postimplant year, during which participants received ITB therapy plus CMM. Standard treatment included physical therapy, occupational therapy, and/or rehabilitation.

The study captured all treatment and other healthcare costs. Costs were estimated in 2003 euros. Costs not available for 2003 were discounted 4% per year according to the Dutch guidelines. To assess the additional health benefits of ITB therapy, the VAS for individual problems and the EQ-5D were administered prior to pump implant and 1 year post implant.

Cost Analysis and Key Conclusions:

Average healthcare costs were €5,296 in the preimplant year and €9,028 in the postimplant year. The mean additional annual healthcare costs for ITB therapy were €3,732. The mean intervention-related costs for ITB therapy, including the screening test, pump implant, and refills, were estimated at €4226 per year.

ITB therapy was more effective and more costly than CMM alone. Using the Dutch EQ-5D index, each additional QALY cost an average of €32,737. Using the UK EQ-5D index, each additional QALY cost an average of €28,273. The average VAS score improved from 2.3 at baseline to 7.2 at 1 year postimplant (P=0.001).

Acronyms: Conventional Medical Management (CMM); Quality-Adjusted Life Year (QALY); Willingness-To-Pay (WTP).

de Lissovoy G, Matza LS, Green H, Werner M, Edgar T. Cost-effectiveness of intrathecal baclofen therapy for the treatment of severe spasticity associated with cerebral palsy. *J Child Neurol.* 2007;22(1):49-59.[78]

An analytic model estimated the incremental cost per QALY over a 5-year period for identical cohorts of children with CP treated with ITB therapy or CMM. Actual treatment costs were obtained from a retrospective analysis of claims data in 2000. Costs for the preimplant year were used to model costs for the alternative treatment group. Costs for the postimplant year were used to model costs for the ITB therapy group during years 2- to 5. All costs were adjusted to the 2003 base year and represented in U.S. dollars. The model also used QALYs obtained from a panel of 9 expert clinicians who used the Health Utilities Index-2 to rate health states associated with treatment. Total annual cost of treatment was based on the amount paid by the insurer. Costs included inpatient and outpatient facility fees, professional fees, pharmacy costs, and home health services. Durable medical equipment was not included.

Cost Analysis and Key Conclusions:

Incremental Cost-effectiveness Ratio: In the base case, ITB therapy cost an average of $49,000 more than CMM over a 5-year period. The average patient receiving ITB therapy experienced a gain of 1.2 QALY during the same time period. Therefore, the net incremental cost-effectiveness ratio (ICER) for ITB therapy was approximately $42,000 per QALY.

Willingness to Pay: It is widely assumed that a treatment that provides an additional QALY at a cost <$50,000 represents a good value for the money. The likelihood that ITB therapy has a cost/QALY of <$50,000 is >70%. Therefore, ITB therapy can be delivered at an acceptable cost.

Sensitivity Analysis: The modeling incorporated treatment scenarios that included adverse events for both the ITB therapy and CMM groups. In one scenario, ITB therapy patients had a 25% annual risk of developing a complication that would increase cost and decrease utility during that year. The ICER would then be $45,700 for ITB therapy.

In a second scenario, the cost for CMM increased 10% annually due to a patient's increasingly complex treatment needs. The ICER for CMM would then be $31,500.

Sampson FC, Hayward A, Evans G, Morton R, Collett B. Functional benefits and cost/benefit analysis of continuous intrathecal baclofen infusion for the management of severe spasticity. *J Neurosurg.* 2002;96(6):1052-1057.[86]

Sampson, et al estimated potential gains in QALYs of ITB therapy by conducting a systematic literature review to identify studies that reported changes in function and/or quality of life measures with at least 6 months mean follow-up. The functional outcomes were related to EQ-5D scores to estimate QALYs. A separate cost analysis was performed using 1999 data from 3 centers in the United Kingdom. Costs represent 1999 U.S. dollars.

Cost Analysis and Key Conclusions:

ITB therapy resulted in functional benefits in carefully selected patients with severe spasticity. The most pronounced benefits were in patients who were bedridden and then able to sit in a wheelchair, and in the small proportion of wheelchair-bound patients who became ambulatory. Other patients also derived benefits from ITB therapy. The cost analysis showed that cost per QALY ranged from $10,550 to $19,570, an acceptable ratio compared to other interventions funded by the health service.

Acronyms: Conventional Medical Management (CMM); EuroQol (EQ-5D); Incremental Cost-Effectiveness Ratio (ICER); Quality-Adjusted Life Year (QALY); Return on Investment (ROI); Visual Analog Scale (VAS).

Postma TJ, Oenema D, Terpstra S et al. Cost analysis of the treatment of severe spinal spasticity with a continuous intrathecal baclofen infusion system. *Pharmacoeconomics*. 1999;15(4):395-404.[85]

A cost analysis of ITB therapy was conducted in the context of a prospective, multicenter, randomized controlled trial in the Netherlands between December 1991 and September 1995. Costs of ITB therapy for 18 patients with severe spasticity due to MS (n=11) or SCI (n=7) were compared to 15 patients matched for disease severity and living circumstances. Cost data was collected from healthcare claims data, hospital registries, and a patient survey. All costs were presented in U.S. dollars but are representative of the Dutch healthcare system.

Cost Analysis and Key Conclusions:

Direct and differential costs: Hospital days per patient were significantly higher in the ITB therapy group during the first year postimplant as compared with the control group (31.5 days vs. 18.7 days, P=0.0002). There was no significant difference between groups in the second year postimplant. The ITB therapy group had significantly higher costs in the implant year (P=0.004) and the second year (P=0.036). The total cost for the first year of ITB therapy was estimated at $28,473 per patient. Total complication costs during the follow-up phase were estimated at $5,439. Savings due to withdrawal of oral medication were estimated to be between $1,950 and $2,800 per year.

Indirect costs: Based on patient interviews and questionnaires, it was determined that the treatment led to an average annual savings (in employment-related costs) of $1,047 per patient. Two patients no longer needed to move to a nursing home after starting treatment, which amounted to an average annual savings of $5,814 per patient.

Ordia JI, Fischer E, Adamski E, Spatz EL. Chronic intrathecal delivery of baclofen by a programmable pump for the treatment of severe spasticity. *J Neurosurg.* 1996;85(3):452-457.[84]

A prospective study evaluated efficacy, safety, and cost-effectiveness of ITB therapy in 59 patients with severe spasticity due to SCI (n=27), MS (n=26), or other etiology (n=6). Results were presented in U.S. dollars and represent cost at the time of the study.

Cost Analysis and Key Conclusions:

During the first year of ITB therapy, the average length of hospitalization was reduced, but there was no reduction in utilization of outpatient resources. During the year prior to pump implant, 10 patients had 12 hospitalizations averaging 7.9 days, for a total of 95 days. Postimplant (excluding the implant procedure), 10 patients had 12 hospitalizations averaging 5.7 days for a total of 68 days. The net result was a reduction of 2.7 hospital days, at $2500/day or $6750/patient per year.

Becker WJ, Harris CJ, Long ML, Ablett DP, Klein GM, DeForge DA. Long-term intrathecal baclofen therapy in patients with intractable spasticity. *Can J Neurol Sci.* 1995;22(3):208-217.[76]

A retrospective chart review reported outcomes and cost analysis of ITB therapy in 9 patients with severe spasticity due to MS (n=6), SCI (n=3), and TBI (n=1). Hospitalization costs for 1 year prior to ITB therapy were compared with hospitalization costs for 1 year with ITB therapy. Results were presented in Canadian dollars and represent cost at the time of the study.

Cost Analysis and Key Conclusions:

Based on a per-day $570 cost of hospitalization, reductions in hospital days with ITB therapy resulted in a mean savings of $31,000 per patient per year. This figure does not include an additional cost of approximately $7,000 for the pump and related equipment, and costs associated with the pump refill procedure. At the time of implant, 6 of 9 patients were institutionalized in either chronic or acute care hospitals due to problems managing spasticity. Following treatment, 3 patients were discharged after prolonged hospitalization. Savings may have been underestimated, as 2 patients were in chronic care institutions prior to implant and thus would not have required acute care.

Acronyms: Multiple Sclerosis (MS); Spinal Cord Injury (SCI); Traumatic Brain Injury (TBI).

Nance P, Schryvers O, Schmidt B, Dubo H, Loveridge B, Fewer D. Intrathecal baclofen therapy for adults with spinal spasticity: therapeutic efficacy and effect on hospital admissions. *Can J Neurol Sci.* 1995;22(1):22-29.[83]

A cost analysis was conducted as part of a prospective study of ITB therapy efficacy for severe spasticity of spinal origin at a center in Canada. The costs of spasticity-related hospitalization for 2 years prior to ITB pump implant were compared with treatment-related hospitalization data for 2 years post- implant. Six of 7 patients who participated in the efficacy trial were included in the cost analysis. Four patients had spasticity due to SCI and 2 due to MS. Costs were represented in Canadian dollars and represent the daily costs of hospitalization in Manitoba at the time of the study.

Cost Analysis and Key Conclusions:

During the 2 years prior to ITB therapy, the 6 patients were hospitalized for spasticity-related reasons for 376 total days, a cost of $305,688. Following initiation of ITB therapy, there were no spasticity-related hospitalizations. However, a total of $110,568 was incurred for the screening phase, implant, and treatment of problems related to the pump and/or ITB therapy. The total cost of the pumps for the 6 patients was $42,000.

When the costs of hospitalization and the pumps were taken into account, there was a total net savings of $153,120 over the 2-year period with ITB therapy.

Steinbok P, Daneshvar H, Evans D, Kestle JR. Cost analysis of continuous intrathecal baclofen versus selective functional posterior rhizotomy in the treatment of spastic quadriplegia associated with cerebral palsy. *Pediatr Neurosurg.* 1995;22(5):255-264.[90]

A retrospective, matched cohort chart review included 19 patients with CP treated with ITB therapy (n=9) or rhizotomy (n=10) in British Columbia. Medical records were reviewed to identify all cost points associated with patient management. Total costs for care were compared between patient groups. Results were presented in Canadian dollars and represent cost at the time of the study.

Cost Analysis and Key Conclusions:

Costs per patient during the first year of ITB therapy were $64,163.10. Costs during the first year following rhizotomy were $16,913.54. The overall costs of ITB therapy were significantly higher than those for rhizotomy, but the populations were not exactly comparable as the patients receiving ITB were generally more severe quadriplegics. The higher cost per patient on ITB therapy was related to the cost associated with screening patients who did not go on to receive an ITB therapy pump, and to additional hospitalization costs for complications in the ITB therapy group.

Meythaler JM, Steers WD, Tuel SM, Cross LL, Haworth CS. Continuous intrathecal baclofen in spinal cord spasticity. A prospective study. *Am J Phys Med Rehabil.* 1992;71(6):321-327.[82]

A prospective study evaluated the safety and efficacy of ITB therapy in 10 patients with severe spasticity due to SCI (n=5), MS (n=1), or other cause (n=4). The authors also compared standard institutional costs of ITB therapy to dorsal root rhizotomy.

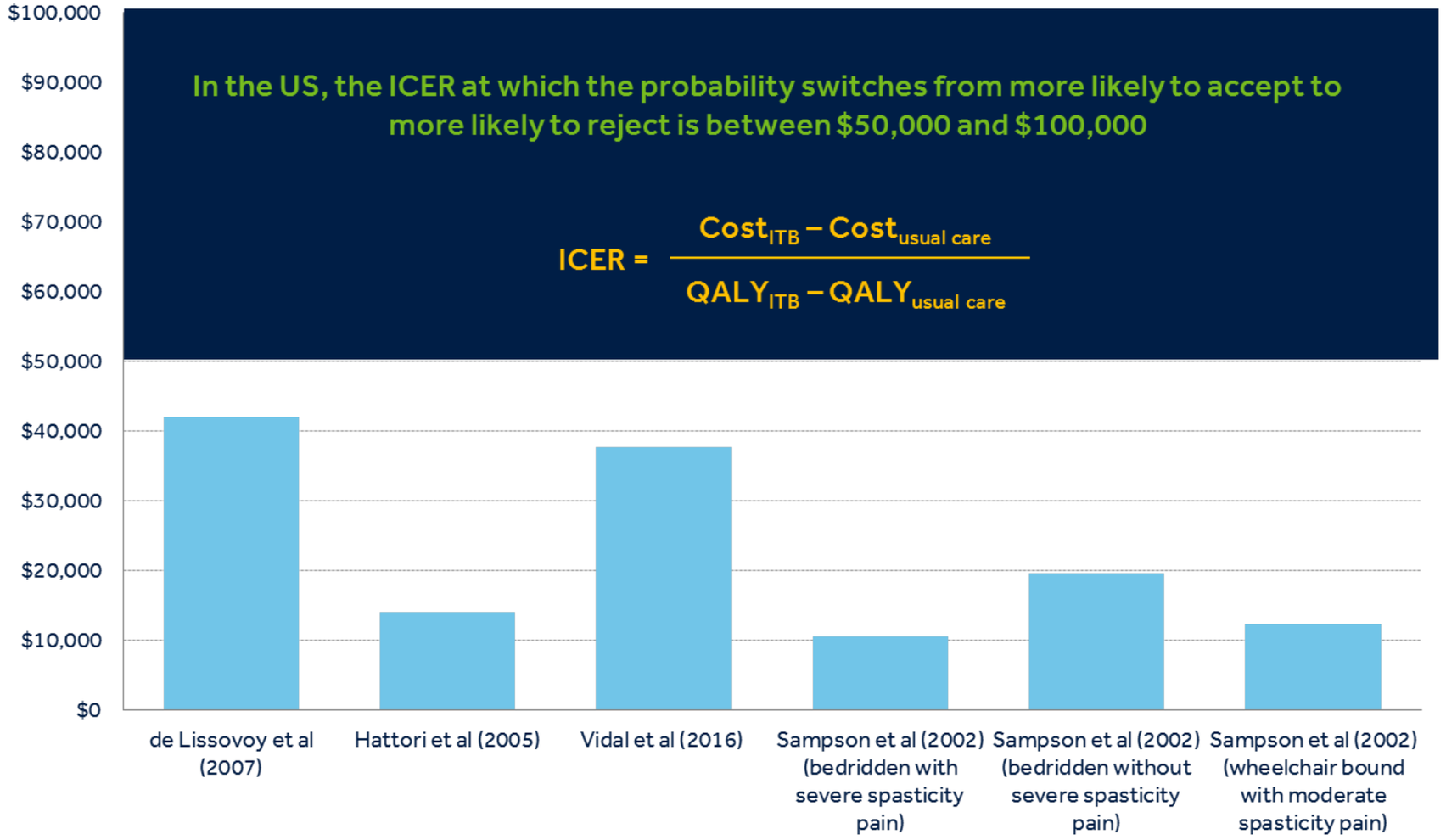
Cost Analysis and Key Conclusions:

Cost analysis included initial hospitalization, surgery, and associated rehabilitation. Costs represent U.S. dollars at the time of the study. At this institution, circa 1992, the mean cost of the ITB therapy implant procedure and 10-day hospitalization was $22,854 (did not include cost of pump or catheter). The mean cost of a dorsal root rhizotomy and 10-day hospitalization was $20,000. The cost for initial pump implant is high but comparable to a dorsal root rhizotomy.

Acronyms: Cerebral Palsy (CP); Intrathecal Baclofen (ITB); Multiple Sclerosis (MS); Spinal Cord Injury (SCI).

INCREMENTAL COST-EFFECTIVENESS RATIO (ICER) OF ITB THERAPY PER QUALITY-ADJUSTED LIFE YEAR (QALY)

Costs are expressed as US dollars. Currencies are converted to 2016 rates.



QALY: An outcome measure taking into account both the quantity (survival) and quality (utility) of life generated by a treatment. QALY = life expectancy x utility

ICER: The incremental cost per QALY is interpreted as the additional cost for 1 additional year of life in full health.

Acronyms: Incremental Cost-Effectiveness Ratio (ICER); Intrathecal Baclofen (ITB); Quality-Adjusted Life Year (QALY); Willingness-To-Pay (WTP).

CLINICAL AND SAFETY EVIDENCE: **CEREBRAL ORIGIN SPASTICITY**

Lead Author	Year	Abbreviated Title	Journal	Page
Cerebral Palsy				
Morton RE	*2011*	Effects of continuous ITB in children with cerebral palsy	*Dev Med Child Neurol*	24
Hoving MA	*2009*	Efficacy of ITB in children with intractable spastic cerebral palsy	*Eur J Paediatr Neurol*	25
Hoving MA	*2009*	Safety and efficacy of ITB in children with cerebral palsy	*Eur J Paediatr Neurol*	26
Vles GF	*2013*	Long-term follow-up on continuous ITB in children with cerebral palsy	*Eur J Paediatr Neurol*	27
Motta F	*2011*	Intrathecal baclofen and motor function in cerebral palsy	*Dev Med Child Neurol*	28
Shilt JS	*2008*	The outcome of ITB on spastic diplegia	*J Pediatr Rehabil*	29
Krach LE	*2006*	Satisfaction of individuals treated long-term with ITB	*Pediatr Rehabil*	30
Ramstad K	*2010*	Continuous ITB in children with cerebral palsy – when does improvement emerge?	*Acta Paediatr*	32
Brochard S	*2009*	Changes in gait following ITB in ambulant children and young adults with cerebral palsy	*Dev Neurorehabil*	33
Albright AL	*2003*	Long-term ITB for severe spasticity of cerebral origin	*J Neurosurg*	34
Motta F	*2007*	The use of ITB implants in children and adolescents: safety and complications	*J Neurosurg Pediatr*	35
Borowski A	*2010*	Complications of ITB pump therapy in pediatric patients	*J Pediatr Ortho*	36
Borowski A	*2008*	Baclofen pump implantation and spinal fusion in children: techniques and complications	*Spine*	37
Ghosh D	*2013*	Complications of ITB in children: experience from a tertiary care center	*Pediatr Neurosurg*	38

Lead Author	Year	Abbreviated Title	Journal	Page
Brain Injury				
Meythaler JM	*1999*	Long-term ITB for spastic-dystonic hypertonia in traumatic brain injury: 1-year experience	*Arch Phys Med Rehabil*	39
Meythaler JM	*1997*	Prospective assessment of ITB for spasticity caused by acquired brain injury: a preliminary report	*J Neurosurg*	40
Ordia JI	*2002*	ITB for the treatment of severe spasticity following traumatic brain injury	*Neuromodulation*	41
Becker R	*1997*	ITB in severe spasticity after traumatic or hypoxic brain injury	*J Neurol*	42
Rawicki B	*1999*	Treatment of cerebral origin spasticity with ITB: long-term follow-up review of 18 patients	*J Neurosurg*	43
Dario A	*2002*	Long-term intrathecal baclofen infusion in supraspinal spasticity of adulthood	*Acta Neurol Scand*	44
Stroke				
Ivanhoe CB	*2006*	Intrathecal baclofen management of poststroke spastic hypertonia: implications for function and quality of life	*Arch Phys Med Rehabil*	45
Schiess MC	*2011*	ITB for poststroke spastic upper and lower extremity motor control and functional improvement	*Neuromodulation*	46
Meythaler JM	*2001*	ITB for spastic hypertonia from stroke	*Stroke*	47
Francisco GE	*2003*	Improvement in walking speed in poststroke spastic hemiplegia after ITB	*Arch Phys Med Rehabil*	48

CONTROLLED STUDY OF THE EFFECTS OF CONTINUOUS INTRATHECAL BACLOFEN INFUSION IN NON-AMBULANT CHILDREN WITH CEREBRAL PALSY [108]

Morton RE, Gray N, Vloeberghs M. *Dev Med Child Neurol.* 2011;53(8):736–741.

OBJECTIVE

This prospective, controlled study of ITB therapy evaluated functional changes in 38 non-ambulatory children with CP (mean age 9 years 11 months). The primary outcome was function in terms of self-care, social skills, and mobility (PEDI). Secondary outcomes were spasticity severity (MAS), spasm frequency (PSFS), gross motor function (GMFM), range of motion, quality of life (Caregiver Questionnaire), and impact of disability (Lifestyle Assessment Questionnaire).

The patients were split into 2 groups. Group 1 (n=18) received conventional medical management (CMM) over a 9 month period and represents baseline data. Group 2 (n=20) received ITB therapy and was evaluated at 9 and 18 months. Comparisons were made between 9 month CMM/baseline outcomes and 9 and 18 month ITB therapy outcomes. Complications were not reported.

RESULTS

Functional Outcomes:

- Variance of change in PEDI was larger than initially predicted. Upon analysis the authors determined that the study was not adequately powered to detect a change in PEDI.

Motor Function and Spasticity Outcomes:

- The ITB group had significantly reduced spasticity severity (MAS) at 9 months ($P = 0.008$) and 18 months ($P = 0.001$) compared to CMM.
- Spasm frequency (PSFS), joint range of motion, and quality of life were significantly improved at 9 months but not 18 months with ITB.
- Range of motion was significantly better in the ITB group at 9 months ($P < 0.005$), but not 18 months, compared to CMM.
- There was no significant difference between the ITB group and CMM group in GMFM.

Quality of Life Outcomes:

- There were no significant differences between the ITB group and CMM group in lifestyle assessment or weight at 9 or 18 months.
- Caregiver questionnaire responses indicated an improvement in comfort, positioning, transfers, and personal care.

Dosing: The mean ITB dose was 216 mcg/day at 9 month assessment and 290 mcg/day at 18 month assessment.

KEY CONCLUSIONS

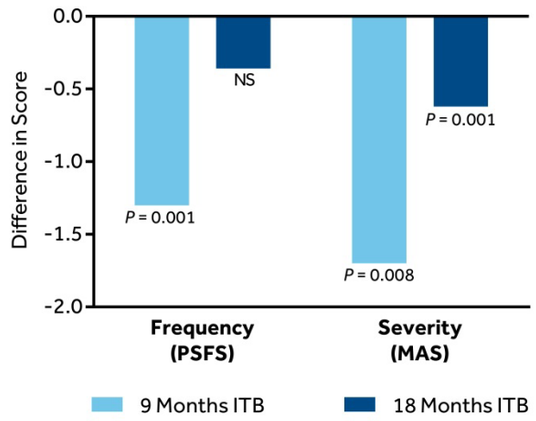
ITB therapy for severe spasticity improves spasticity frequency and severity, and patient/caregiver ease of care, in non-ambulant children with CP. ITB therapy has less effect on function, societal participation, or cost of new equipment.

Limitations: Group 1 (CMM) was, on average, slightly more able than Group 2 (ITB therapy) in terms of initial PEDI and GMFM scores. This is because several patients in Group 2 had very severe disabilities. The difference between groups may have reduced the detection of improvement with ITB and could not be completely corrected by ANCOVA statistical analysis.

The PEDI scale was used as a primary outcome measure. The authors found that this assessment was not appropriate for children with severe disabilities because they are dependent on their caregivers, while the PEDI assesses functional capabilities.

DIFFERENCE IN MEAN SPASTICITY SCORE, GROUP 2 – GROUP 1

(negative change indicates improvement)



Acronyms: Analysis of Covariance (ANCOVA);Cerebral Palsy (CP); Conventional Medical Management (CMM); Gross Motor Function Measure (GMFM); Modified Ashworth Scale (MAS); Pediatric Evaluation of Disability Inventory (PEDI); Penn Spasm Frequency Scale (PSFS).

EFFICACY OF INTRATHECAL BACLOFEN THERAPY IN CHILDREN WITH INTRACTABLE SPASTIC CEREBRAL PALSY: A RANDOMISED CONTROLLED TRIAL [101]

Hoving MA, van Raak EP, Spincemaille GH, Palmans LJ, Becher JG, Vles JS; Dutch Study Group on Child Spasticity. *Eur J Paediatr Neurol.* 2009;13(3):240–246.

OBJECTIVE

A prospective, randomized, parallel-controlled design evaluated ITB therapy against conventional medical management (CMM) in 17 children with severe spasticity due to CP (mean age 13. 2 years). Primary outcome measures were three individually formulated problems per child using a VAS, and the caregiver assistance scale in the self-care domain of the PEDI at 6 months. Secondary outcome measures were motor function (GMFM), spasticity severity (AS), CP-specific health-related quality of life (CHQ-PF50), and the functional skills scale in the self-care domain of the PEDI. Outcome measure changes from baseline to 6 month follow-up were evaluated for the ITB group (n=9) and the CMM group (n=8). Complications were not reported

RESULTS

Quality of Life and Caregiver Outcomes:

- There was no significant difference between groups in the PEDI self-care domain.
- VAS individual problem outcomes showed greater improvement in the ITB group compared to the CMM group at 6 months. The average of all VAS individually formulated problems significantly improved in the ITB group ($P = 0.001$). The most frequently reported problems, ease of care and pain, were separately analyzed and significantly improved in the ITB group ($P = 0.008$ and $P = 0.016$, respectively).
- Four of 12 health-related quality of life measures were significantly improved in the ITB group compared to CMM: bodily pain/discomfort ($P = 0.014$), mental health ($P = 0.045$), parental impact-time ($P = 0.043$), and psychosocial summary score ($P = 0.027$). There was not a significant difference in the other measures.
- There was no significant improvement in the PEDI functional skills scale with ITB therapy.

Motor Function and Spasticity Outcomes:

- Motor function (GMFM) was significantly better in the ITB group compared to the CMM group ($P = 0.028$).
- In 22 muscle group measurements, spasticity severity significantly improved in the ITB group compared to CMM for right wrist flexors ($P = 0.038$), left hip adductors ($P = 0.025$), and both hip flexors (right $P = 0.022$, left $P = 0.043$).

Dosing: Mean ITB dose was 67 mcg/day after implant and 176 mcg/day at 6 months.

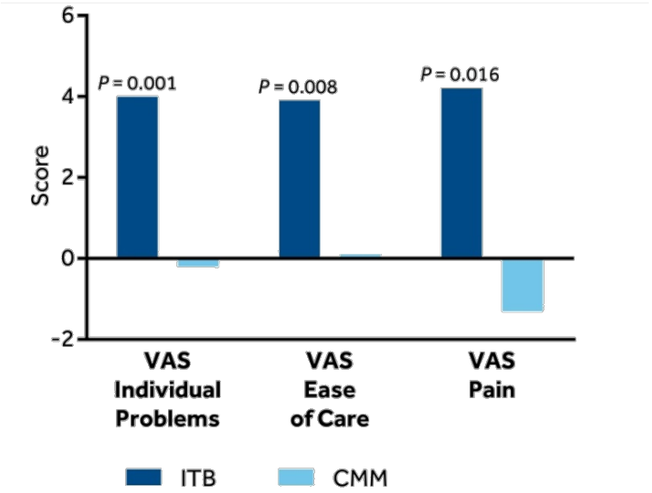
KEY CONCLUSIONS

ITB therapy appears to decrease spasticity severity, improve motor function, and improve individually formulated problems including pain and ease of care, as compared to conventional medical management for severe spasticity due to CP.

Limitations: Fourteen of 17 children were GMFCS level V, which indicates they had physical disabilities restricting voluntary control and were impaired in all areas of motor function. These patient characteristics may have hindered the ability of the PEDI self-care domain to assess changes with ITB. Neither participants nor investigators were blinded to the group assignment. Generalizability is limited to older children (mean age was 13.2 years) who rely on wheeled mobility.

MEAN CHANGE IN VAS SCORE AT 6 MONTHS

(positive score indicates improvement)



Acronyms: Ashworth Scale (AS); Cerebral Palsy (CP); Child Health Questionnaire™ Parent Form (CHQ-PF50); Conventional Medical Management (CMM); Gross Motor Function Measure (GMFM); Pediatric Evaluation of Disability Index (PEDI); Visual Analog Scale (VAS).

SAFETY AND ONE-YEAR EFFICACY OF INTRATHECAL BACLOFEN THERAPY IN CHILDREN WITH INTRACTABLE SPASTIC CEREBRAL PALSY [102]

Hoving MA, van Raak EP, Spincemaille GH et al; Dutch Study Group on Child Spasticity. *Eur J Paediatr Neurol.* 2009;13(3):247-256.

OBJECTIVE

This study is a prospective, uncontrolled continuation of the 6 month RCT.[101] Seventeen children with severe spasticity due to CP (mean age 13.7 years) were treated with ITB therapy and evaluated for 12 month efficacy and 24 month safety. Efficacy outcomes matched the 6 month RCT. Primary outcomes were 3 individually-formulated problems per child (VAS) and the caregiver assistance scale in the PEDI self-care domain. Secondary outcomes were motor function (GMFM), spasticity severity (AS), CP-specific health-related quality of life (CHQ-PF50), the functional skills scale in the PEDI self-care domain, and 24-month adverse events.

RESULTS

Quality of Life and Caregiver Outcomes:

- There was no significant improvement in the PEDI self-care domain.
- The average of all VAS individually-formulated problems significantly improved compared to baseline ($P = 0.000$). Ease of care and pain were the most frequently reported problems and were separately analyzed; both significantly improved compared to baseline (ease of care, $P = 0.000$; pain, $P = 0.002$).
- Significant improvement was observed in 3 of 12 CHQ-PF50 measures: bodily pain/discomfort ($P = 0.016$), mental health ($P = 0.007$), and psychosocial summary ($P = 0.088$).

Motor Function and Spasticity Outcomes:

- Motor function significantly improved in the GMFM sitting ($P = 0.022$) and goal ($P = 0.007$) dimensions. Mean overall GMFM score was not significantly improved from baseline; since 14 of the 17 patients were quadriplegics, the walking, crawling, and standing dimensions were largely unaffected.
- Spasticity significantly decreased in 5 of 8 upper extremity ($0.008 \leq P \leq 0.046$) and 9 of 14 lower extremity muscle groups ($0.002 \leq P \leq 0.046$).

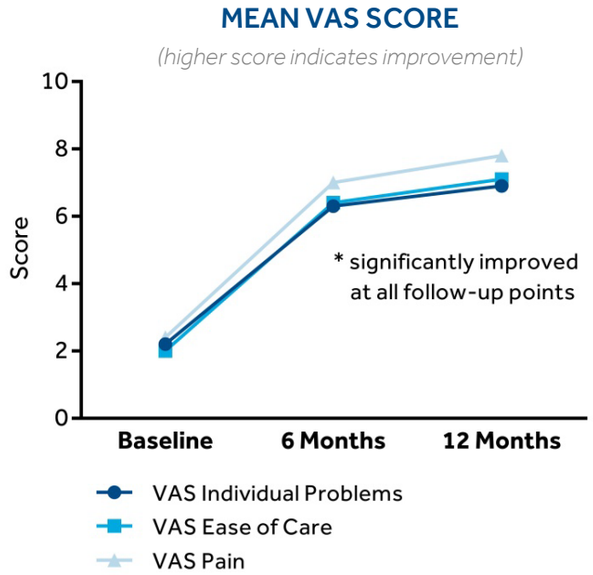
Dosing: The mean ITB dose was 61 mcg/day at implant, 189 mcg/day at 6 months, and 233 mcg/day at 12 months. Six of 7 patients who used oral baclofen discontinued use during the first 10 postoperative days.

Adverse Events: At a mean follow-up of 18.4 months, the incidence of procedure and device-related adverse events was 0.09 per patient month and 0.16 per patient month for non-procedure or device related events. Five non-procedure/device-related events were considered serious as they resulted in significant disability: difficulty swallowing (n=1), dysarthria (n=1), excessive hypotonia (n=2), and epileptic seizure (n=1). These complications did not require hospitalization. Serious procedure/device related complications requiring surgical management were incomplete catheter implant requiring reoperation (n=8), abrupt loss of efficacy requiring catheter replacement (n=4), and pain requiring pump repositioning (n=2).

KEY CONCLUSIONS

ITB therapy efficacy for spasticity, motor function, and individually formulated problems was sustained through 12 months and well accepted; 15 children or caregivers said they would participate in all procedures again. The majority of children found that they could extend their activities and participation in social activities with improvement in pain and spasticity.

Limitations: Generalizability is limited to older children (mean age was 13.2 years) who rely on wheeled mobility.



Acronyms: Ashworth Scale (AS); Cerebral Palsy (CP); Child Health Questionnaire™ Parent Form (CHQ-PF50); Gross Motor Function Measure (GMFM); Pediatric Evaluation of Disability Inventory (PEDI); Randomized Controlled Trial (RCT); Visual Analog Scale (VAS).

LONG-TERM FOLLOW-UP ON CONTINUOUS INTRATHECAL BACLOFEN THERAPY IN NON-AMBULANT CHILDREN WITH INTRACTABLE SPASTIC CEREBRAL PALSY [116]

Vles GF, Soudant DL, Hoving MA et al. *Eur J Paediatr Neurol.* 2013;17(6):639-644.

OBJECTIVE

This study is a long-term prospective follow-up of 17 children who had participated in the 6 month RCT[101] and 12 month continuation study[102] published by Hoving et al. Mean age at time of inclusion was 13 years 2 months. Quality of life and caregiver perception of ITB therapy was assessed in non-ambulant children with severe spasticity due to CP using the quality-of-life Child Health Questionnaire (CHQ-PF50) and VAS for caregivers' satisfaction. Long-term assessments, done 6 to 9 years after the original study, were compared to the data collected at baseline and 12 months after starting ITB therapy.

RESULTS

Long-term Quality of Life and Caregiver Outcomes:

Previously identified positive effects remained significantly improved over baseline:

- Pain was significantly improved as measured by the CHQ ($P = 0.002$) and the VAS ($P = 0.02$).
- Ease of care (VAS) significantly improved ($P = 0.00$).
- Mental health (CHQ) significantly improved ($P = 0.010$).

Previously non-significant CHQ dimensions became significant at 6-9 years after starting ITB therapy:

- Parental impact–emotional significantly improved ($P = 0.008$).
- Parental impact–time significantly improved ($P = 0.002$).
- Physical summary significantly improved ($P = 0.019$).

Caregivers rated improvement or worsening of functioning for 40 domains on a 5-point scale. Improvement in functioning with long-term ITB therapy was reported more frequently than worsening in all domains except drooling and bladder control. Improvements were most frequently noted for ability to transfer, startle movements and sudden jerks, and sleeping at night. Caregivers for 16 of 17 children (94%) reported that they would choose ITB therapy again.

Adverse Events: Complications with long-term ITB therapy were: pain caused by pump (n=2), pump failure (n=1), pump subsidence/movement (n=1), catheter problems (catheter too high n=2, catheter too low n=1, catheter too superficial n=1, catheter obstructed n=1), and refill-related problems (n=3). There were 28 total hospitalizations, range 1-4 per child, mainly for pump replacement. Four of 17 children underwent orthopedic surgery while receiving ITB therapy (surgical correction of scoliosis interventions n=3, fibular tendon lengthening n=1).

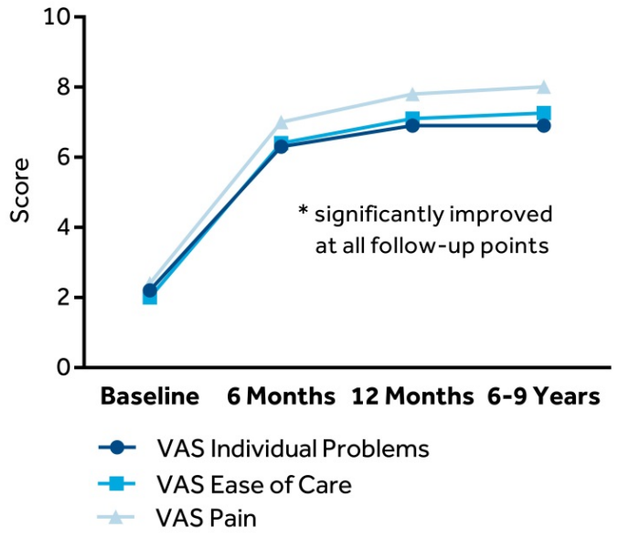
KEY CONCLUSIONS

At 6-9 years follow-up of ITB therapy outcomes, improvements in spasticity-related pain, ease of care, and mental health were maintained and new improvements in parental impact scales were observed.

Limitations: The open-label uncontrolled nature of this study limits firm conclusions on the long-term effects of ITB therapy, particularly the previously non-significant changes in CHQ dimensions. Questionnaires were not completed by the patients themselves but by their caregivers. The caregiver questionnaire (Staal et al) has not been validated.

MEAN VAS SCORE

(higher score indicates improvement)



Acronyms: Cerebral Palsy (CP); Child Health Questionnaire™ Parent Form (CHQ-PF50); Visual Analog Scale (VAS).

INTRATHECAL BACLOFEN AND MOTOR FUNCTION IN CEREBRAL PALSY [109]

Motta F, Antonello CE, Stignani C. *Dev Med Child Neurol.* 2011;53(5):443–448.

OBJECTIVE

Motor function, spasticity, and functionality were retrospectively evaluated in 37 patients with CP (mean age at implant 13 years 7 months) receiving ITB therapy. Thirty (30) of the patients had spastic CP. Outcomes, measured at baseline and 12 months, were gross motor function (GMFM), spasticity severity (MAS), and a patient/caregiver questionnaire.

RESULTS

Spasticity and Motor Function Outcomes: Spasticity was significantly reduced at 12 months with ITB therapy ($P < 0.001$). Gross motor function (GMFM) significantly improved at 12 months with ITB therapy.

- Median total GMFM score was significantly improved in all 30 patients with spastic CP ($P = 0.004$).
- When analyzed according to degree of impairment (GMFCS levels II-III vs. levels IV-V), ITB therapy improved median total GMFM score for both groups ($P < 0.05$ for levels II-III, $P < 0.001$ for levels IV-V).
- Motor function analysis by age showed significantly better improvement in patients less than 18 years old ($P < 0.05$). When analyzed according to age group (<8 years, n=10; 8-18 years, n=18; >18 years, n=9), median total GMFM scores significantly improved in the two younger age groups (<8 years, $P = 0.007$; 8-18 years, $P = 0.018$) but not in the >18 years age group.

Functional Outcomes: By subjective questionnaire, most patients/caregivers reported improved transfers, care management, seat position, endurance, and walking. There were no reports of worsened performance with ITB therapy. Thirty-five patients were satisfied and 2 were undecided.

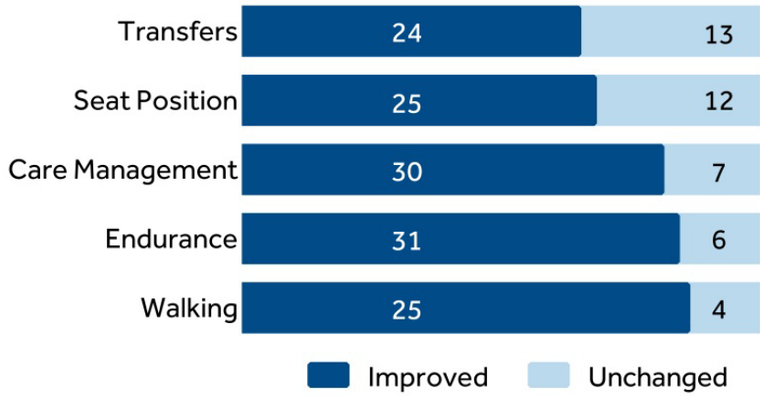
Adverse Events: Four patients experienced major complications during follow-up: catheter-related (n=3) requiring replacement, infection (n=1) which resolved with antibiotic treatment, and CSF leak (n=1) which resolved without intervention. There were no drug-related complications.

KEY CONCLUSIONS

Patients with mild to moderate impairment (GMFCS levels II-III) showed the most improvement in walking, while patients with severe impairment (GMFCS levels IV-V) had the most improvement in care management. Patients who were younger than 18 years of age showed the most improvement in motor function. These results suggest that ITB therapy can benefit both ambulant and non-ambulant patients with CP.

Limitations: Interpretation of results is limited due the study's small sample size, retrospective data collection, and lack of a control group.

SUBJECTIVE QUESTIONNAIRE RESPONSES



Acronyms: Cerebral Palsy (CP); Cerebrospinal Fluid (CSF); Gross Motor Function Classification System (GMFCS); Gross Motor Function Measure (GMFM); Modified Ashworth Scale (MAS); Visual Analog Scale (VAS).

THE OUTCOME OF INTRATHECAL BACLOFEN TREATMENT ON SPASTIC DIPLEGIA: PRELIMINARY RESULTS WITH A MINIMUM OF TWO YEAR FOLLOW-UP [115]

Shilt JS, Reeves S, Lai LP et al. *J Pediatr Rehabil Med.* 2008;1(3):255–261.

OBJECTIVE

Functional ability and quality of life were evaluated in a prospective study of ITB therapy in 8 children (mean age 7.9 years) with severe spasticity due to diplegic CP. All patients were GMFCS III or IV signifying decreased functional ability at baseline. Physical and functional outcomes included spasticity severity (AS), gait (PRS), and disability (WeeFIM). Health-related quality of life was evaluated using the SF-36, CES-D short form, Impact on Family Scale, Life Orientation Test, Rand Social Support Survey, and Social Desirability Scale. Complications were not reported.

RESULTS

Spasticity and Gait Outcomes:

Median Ashworth scores were reduced in all extremities after 18 months of ITB therapy.

- Hip adductors, knee flexors, knee extensors, and ankle plantar extensors improved significantly (all $P < 0.03$).

Several components of the PRS demonstrated an improvement in ambulation after 18 months of ITB therapy. There was not a significant change from baseline in total median PRS score.

- Significant improvements were observed in gait ($P = 0.05$), hind foot strike ($P = 0.05$), knee position ($P = 0.03$), and hind foot gait ($P = 0.05$) with ITB therapy. Crouch and speed were not significantly improved.

Functional Outcomes: Total median WeeFIM score, representing locomotion and transfer, significantly improved at 18 months ($P = 0.03$). There was improvement in individual measures for toilet ($P = 0.05$) and walking ($P = 0.02$).

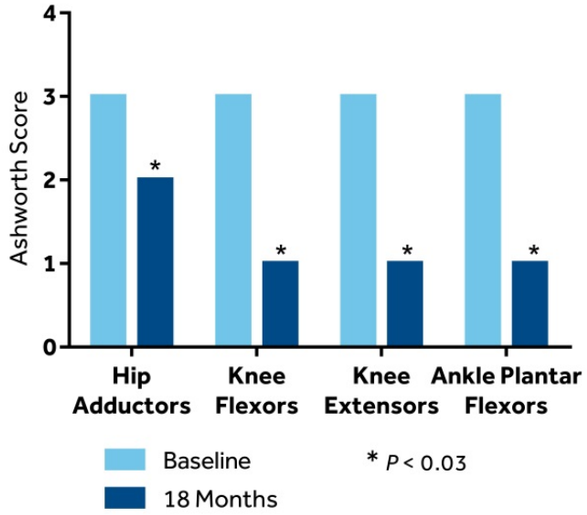
Parent/Caregiver Health-Related Quality of Life Outcomes: At the most recent follow-up, parent/caregiver health-related quality of life scores did not change significantly from baseline in any measure.

KEY CONCLUSIONS

The results suggest that ITB therapy improves spasticity and function, and does not hinder ambulation in patients with diplegic CP.

Limitations: Interpretation of results is limited by the study's small sample size and uncontrolled open-label follow-up. The health-related quality of life measures have not been validated for this specific patient group.

MEDIAN ASHWORTH SCORES



Acronyms: Ashworth Scale (AS); Center for Epidemiologic Studies Depression Scale (CES-D); Cerebral Palsy (CP); Pediatric Functional Independence Measure (WeeFIM); Gross Motor Function Classification System (GMFCS); Physician Rating Scale (PRS); Short Form Survey (SF-36).

SATISFACTION OF INDIVIDUALS TREATED LONG-TERM WITH CONTINUOUS INFUSION OF INTRATHECAL BACLOFEN BY IMPLANTED PROGRAMMABLE PUMP [104]

Krach LE, Nettleton A, Klempka B. *Pediatr Rehabil.* 2006;9(3):210–218.

OBJECTIVE

In a retrospective study, 100 patients or caregivers were interviewed about their satisfaction with ITB therapy. Patient age ranged from 5 to 42 years (mean 15 years) and all patients had severe spasticity due to CP (n=88) or other causes (n=12). Over 80% of patients were GMFCS levels IV or V with significant motor impairment. Interviews explored perceptions regarding the impact of ITB therapy on activities of daily living (ADLs) and overall satisfaction with ITB therapy. The mean treatment duration was 2.6 years.

RESULTS

Goals and overall satisfaction: Goal achievement was fully met in 71% and partially met in 14% of patients. Most patients or caregivers favored ITB therapy, as 82% would choose ITB therapy again. The groups of patients/caregivers that reported they would not choose ITB therapy again, or were uncertain, had a lower frequency of fully met goals: 15.8% compared to 71% in the total group.

Adverse Events: Thirty-two patients experienced 22 device or procedure-related complications: catheter obstruction, migration, or fracture (n=12), post-operative infection requiring explant and re-implant (n=6), catheter-pump connector tear (n=7), and catheter tip repositioning (n=1).

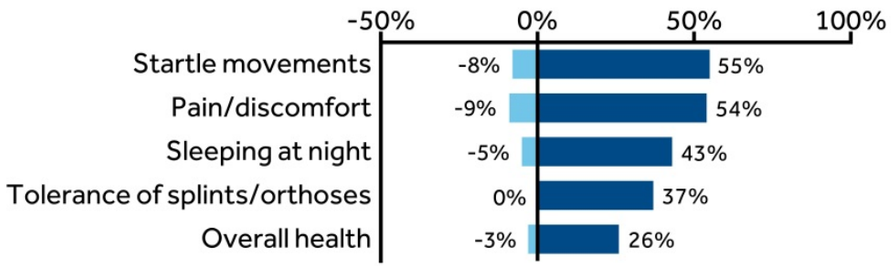
KEY CONCLUSIONS

As rated by patients and caregivers, ITB therapy improved patients' motor skills, level of comfort, ease of care, and ability to participate in ADLs. Motor skills that required lower extremity tone (ability to transfer and position, walking, toileting, and dressing) had the highest frequency of improvement.

Limitations: The study participants were asked to recall aspects of ITB therapy impact from 1-3.75 years prior to the interview (recall bias). The interview scales are based on previous publications but are not validated. The respondents were patients, or caregivers when youth or impairment prevented patient response. There was no comparative interview group that did not receive ITB therapy.

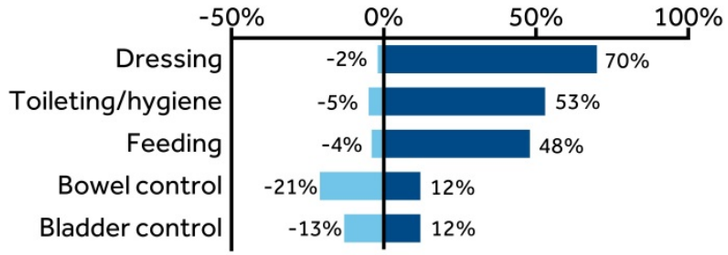
LEVEL OF COMFORT

(positive score indicates improvement, remaining proportion is no change)



SELF-CARE

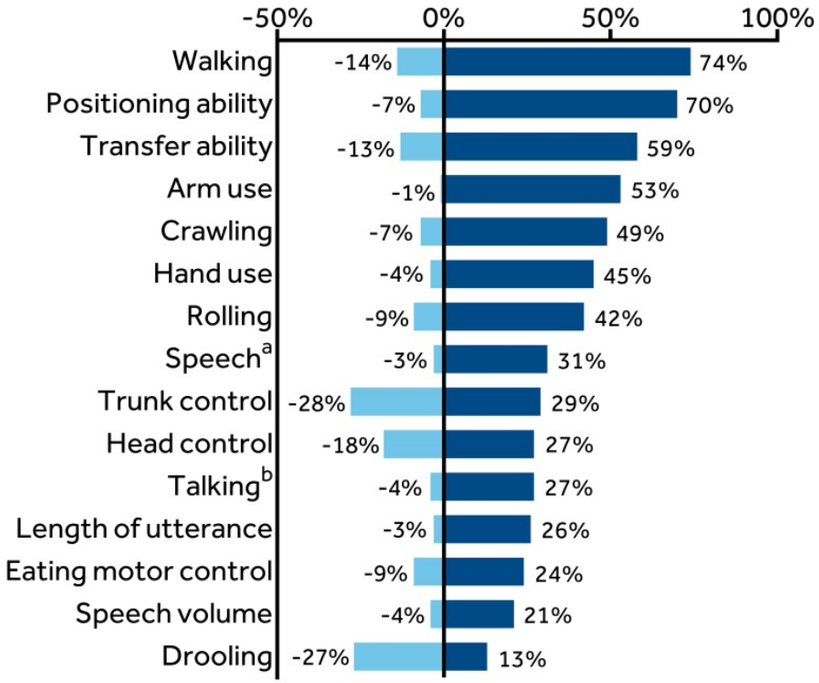
(positive score indicates improvement, remaining proportion is no change)



Acronyms: Activities of Daily Living (ADLs); Cerebral Palsy (CP); Gross Motor Function Classification System (GMFCS).

MOTOR SKILLS

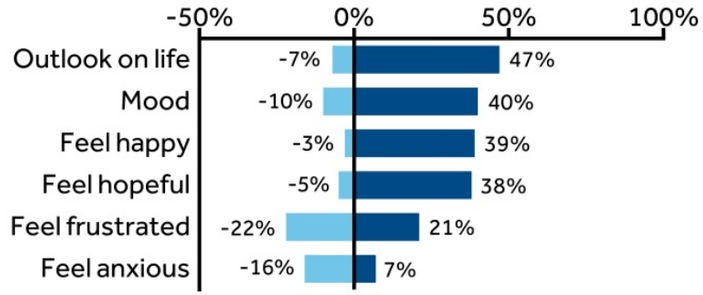
(positive score indicates improvement, remaining proportion is no change)



[a] Cooing, vocalizing, babbling
[b] Speech clarity

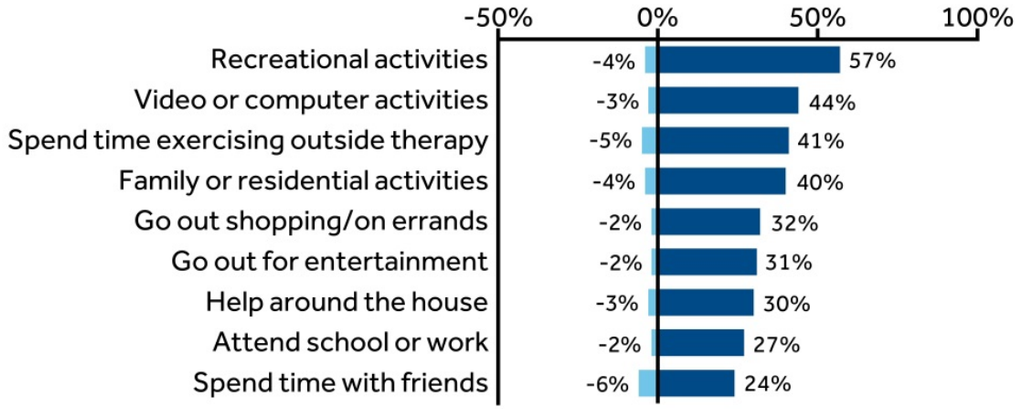
EMOTIONS

(positive score indicates improvement, remaining proportion is no change)



PARTICIPATION IN ACTIVITIES

(positive score indicates improvement, remaining proportion is no change)



CONTINUOUS INTRATHECAL BACLOFEN THERAPY IN CHILDREN WITH CEREBRAL PALSY – WHEN DOES IMPROVEMENT EMERGE? [112]

Ramstad K, Jahnsen R, Lofterod B, Skjeldal OH. *Acta Paediatr.* 2010;99(11):1661–1665.

OBJECTIVE

In a prospective study, 35 children receiving ITB therapy for severe spasticity due to CP were followed for 18 months. Patients were median 10.8 years at pump implant and predominantly GMFCS levels IV or V. Spasticity severity (MAS), gross motor function (GMFM), patient functional skills and caregiver impact (PEDI), and pain episodes and nighttime awakenings (parent questionnaire) were evaluated after 6 and 18 months of ITB therapy. Complications were not reported.

RESULTS

Spasticity and Motor Function Outcomes:

- Though knee flexor spasticity (MAS) was not improved at 6 months, there was a significant improvement at 18 month follow-up ($P = 0.022$).
- Motor function (GMFM) was significantly improved at 6 months ($P = 0.032$) and 18 months ($P = 0.005$).

Functional Skills and Caregiver Assistance Outcomes:

- On both PEDI Functional Skills and Caregiver Assistance Scales, social function significantly improved in the first 6 months of ITB therapy ($P \leq 0.05$) through 18 month follow-up ($P \leq 0.01$) as compared to baseline.
- Mobility domain scores in the PEDI Functional Skills Scale were decreased at 6 months, yet significantly increased/improved at 18 months as compared to baseline ($P < 0.05$).

Sleep and Spasticity-Related Pain Outcomes:

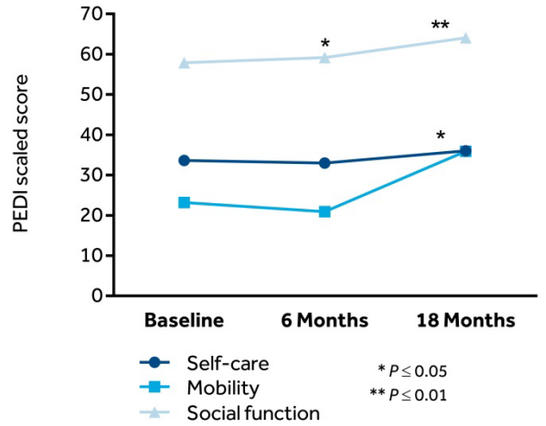
- Nighttime awakenings stopped by 6 months and remained stopped at 18 months ($P \leq 0.01$).
- Pain frequency and severity decreased significantly by 6 months (both $P \leq 0.01$) and remained so at 18 months (frequency $P \leq 0.01$, severity $P \leq 0.05$).

KEY CONCLUSIONS

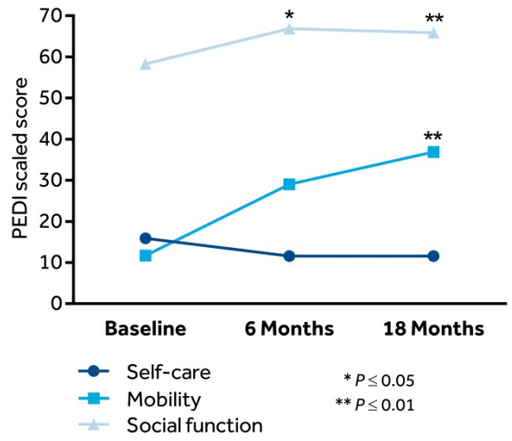
ITB therapy improved motor and social function in severely disabled children with CP. Improvements may occur slowly as therapy is titrated.

Limitations: The data consisted of small patient numbers and distributions with extreme values, limiting statistical inferences. Additionally, results are weakened by missing data.

MEDIAN PEDI FUNCTIONAL SKILLS SCORES



MEDIAN PEDI CAREGIVER ASSISTANCE SCORES



Acronyms: Cerebral Palsy (CP); Modified Ashworth Scale (MAS); Gross Motor Function Measure (GMFM); Pediatric Evaluation of Disability Inventory (PEDI).

CHANGES IN GAIT FOLLOWING CONTINUOUS INTRATHECAL BACLOFEN INFUSION IN AMBULANT CHILDREN AND YOUNG ADULTS WITH CEREBRAL PALSY [97]

Brochard S, Lempereur M, Filipetti P, Rémy-Néris O. *Dev Neurorehabil.* 2009;12(6):397–405.

OBJECTIVE

A retrospective case series assessed the medium-term effects of ITB therapy on clinical, functional, and quantitative gait parameters of 7 ambulant children and young adults with CP (mean age 15 years, range 9-22 years). All patients were evaluated prior to starting and at 16 months of ITB therapy. Measured outcomes included spasticity severity (AS), muscle contractures (maximal joint angles), functional gait status/ambulation (Gillette FAQ), and gait pattern (Gillette Gait Index and 3D gait analysis).

RESULTS

Spasticity and Contracture Outcomes:

- Spasticity severity (AS) was significantly reduced from 3.04 to 1.89 ($P < 0.05$). Reduction of spasticity was greater in rectus femoris (-1.86, $P = 0.02$) and adductor magnus (-1.28, $P = 0.04$) than hamstring (-0.71, not significant) and triceps surae (-0.85, not significant).
- A significant increase in rectus femoris joint angle was observed (+17.14, $P = 0.02$), but no significant difference was measured in other muscle groups.

Gait Outcomes:

- Functional gait status (Gillette FAQ) significantly improved from 6.10 to 7.10 ($P = 0.02$).
- Mean step length significantly improved from 0.65 meters to 0.74 meters ($P < 0.05$). There was no significant improvement in mean Gillette Gait Index. This score, which contains spatiotemporal and kinematic parameters and evaluates overall gait, worsened in 3 patients and improved in 4 patients. There was no significant change in mean gait speed, step time, stance phase, or cadence.
- Minimum hip flexion angle at stance phase significantly decreased from 19.82 degrees to 8.3 degrees ($P < 0.01$).
- Hip flexion at terminal stance significantly decreased from 32.25 degrees to 21.58 degrees ($P = 0.01$).

Dosing: Mean dose at follow-up was 121.80 mcg/day (range 75-250 mcg/day).

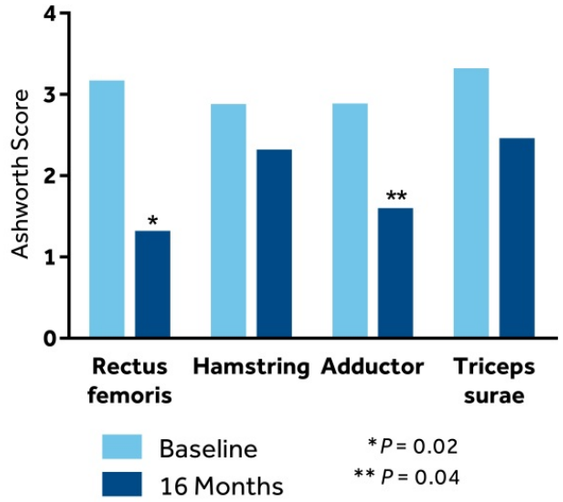
Adverse Events: One patient developed a cutaneous hematoma and one patient had a catheter disconnection requiring surgery.

KEY CONCLUSIONS

ITB therapy appears to improve spasticity and the functional gait capacity of ambulant children with cerebral palsy. Kinematic changes with ITB therapy were different for each child, yet there was a global trend toward proximal joint extension possibly indicating an improved swing phase and gait pattern. The authors did not observe a crouching effect or significant worsening of other gait parameters.

Limitations: The study enrolled a small number of patients. It was retrospectively conducted but data was collected prospectively.

MEAN ASHWORTH SCORES



Acronyms: Ashworth Scale (AS); Cerebral Palsy (CP); Gillette Functional Assessment Questionnaire (Gillette FAQ).

LONG-TERM INTRATHECAL BACLOFEN THERAPY FOR SEVERE SPASTICITY OF CEREBRAL ORIGIN [93]

Albright AL, Gilmartin R, Swift D et al. *J Neurosurg.* 2003;98(2):291-295.

OBJECTIVE

A prospective, open-label, multicenter study assessed the long-term effectiveness, safety, and dosing of ITB therapy in 68 patients with severe spasticity due to CP (n=54), BI (n=9), or other (n=5); mean age at implant 12.6 years. Participants were a subset of patients in the initial randomized controlled clinical investigations of ITB therapy for cerebral origin spasticity. The primary outcomes were upper and lower extremity spasticity severity (AS), ITB dose, and complications. Patients were expected to return for evaluation at least every 90 days for at least 3 years. The mean follow-up was 70 months.

RESULTS

Spasticity Outcomes: Ashworth scores improved significantly from baseline. For the upper extremities, change from baseline was significant at 6, 12, and 24 months (all $P < 0.001$). For the lower extremities, change from baseline was significant at each 6-month interval through 36 months (all $P < 0.0001$). While the number of patients followed for 7-10 years was small, the average AS scores were similar to those observed during the first 6 years.

Dosing: The mean ITB dose at 3 months was 157 mcg/day. Dosage increased gradually over the first 1 to 3 years to a mean 300 mcg/day, with little variance thereafter. There was no significant difference in daily dose between children, adolescents, and adults.

Adverse Events: Two-thirds of the patients experienced an adverse event during follow-up. A total of 87 adverse events were reported during the titration phase and 132 during the maintenance phase. Infection occurred in 3 patients, requiring explant. Two deaths occurred during the follow-up period. Both were believed to be unrelated to ITB therapy or the function of the pump.

KEY CONCLUSIONS

ITB therapy provided long-term reduction in severe upper and lower extremity spasticity with a relatively stable dosing profile. The most common complications were drug-related, which were reported in up to 25% of patients during the maintenance phase.

Limitations: The number of patients with data at 7 to 10 years was too small for statistical analysis.

DEVICE-RELATED COMPLICATIONS IN >5% OF PATIENTS

Complication	No. of Events (% of Patients)
Procedure-related	
Pocket seroma	15 (16.2%)
CSF leak	13 (14.7%)
System-related	
Catheter fracture/break	12 (16.2%)
Catheter kink/occlusion	7 (8.8%)
Pocket seroma	6 (7.4%)
Catheter dislodged	4 (5.9%)

POTENTIAL DRUG-RELATED COMPLICATIONS IN >5% OF PATIENTS

Complication	No. of Patients with Complications (%)	
	Titration Phase (up to 60 days postimplant)	Maintenance Phase (>60 days postimplant)
Hypotonia	12 (17.6%)	17 (25.0%)
Somnolence	11 (16.2%)	13 (19.1%)
Convulsions	3 (4.4%)	9 (13.2%)
Nausea and vomiting	8 (11.8%)	0 (0.00%)
Headache	7 (10.3%)	1 (1.5%)

Acronyms: Ashworth Scale (AS); Brain Injury (BI); Cerebral Palsy (CP); Cerebrospinal Fluid (CSF).

THE USE OF INTRATHECAL BACLOFEN PUMP IMPLANTS IN CHILDREN AND ADOLESCENTS: SAFETY AND COMPLICATIONS IN 200 CONSECUTIVE CASES [110]

Motta F, Buonaguro V, Stignani C. *J Neurosurg Pediatr.* 2007;107:32–35.

OBJECTIVE

A retrospective chart review evaluated safety and complications of ITB therapy at a children's hospital in Italy. The review included 200 pediatric patients with severe spasticity due to CP (n=175), or other causes (n=25). Sixty-two patients (31%) had at least 1 complication for a total of 75 complications; an incidence of 1 complication every 11.3 years of treatment.

RESULTS

Adverse Events: Infection developed in 20 patients (10%), and 15 patients required explant. Infection rates decreased over time, from 10% (1998– 2000) to 6.9% (2001–2002) to 4.8% (2003–2005). The decreased infection rate was statistically correlated to the adoption of subfascial pump placement and pre-surgical antibiotic prophylaxis (odds ratio not provided).

CSF leaks developed in 34 patients (17%), with one patient eventually requiring explant. Patients younger than 10 years of age were more likely to develop CSF leaks (Odds Ratio 3.07, $P = 0.009$).

The pump was explanted in 24 patients (12%) due to complications. Severe complications such as CSF leak and infection were the reason for explant in 16 (8%), and patient/parent dissatisfaction was the reason for explant in 8 patients (4%).

KEY CONCLUSIONS

GMFCS Level V was the largest group (n=73) with the lowest mean age, most impairment, and highest incidence of complications (13.0%). The onset of at least 1 complication appeared to be statistically correlated with AS scores greater than 3 and an age of 10 years or younger ($P < 0.050$). There was no correlation between complication rate and patient weight, ambulatory status, or the presence of dystonia or cerebral palsy.

COMPLICATIONS BY GMFCS LEVEL

GMFCS Level	No. of Patients	No. of Patients with Complications	Total Complications
I	2 (1.0%)	1 (0.5%)	2
II	4 (2.0%)	1 (0.5%)	1
III	33 (16.5%)	9 (4.5%)	12
IV	63 (31.5%)	19 (9.5%)	22
V	73 (36.5%)	26 (13.0%)	34
Not CP	25 (12.5%)	6 (3.0%)	9

COMPLICATIONS BY TYPE AND TIME PERIOD

		No. of Patients with Complications				
Time Period	No. of Patients	Total Complications	Infection Only	CSF Leak Only	Catheter Complications	> 1 Complication
1998–2000	80	31 (38.8%)	8 (10.0%)	12 (15.0%)	6 (7.5%)	5 (6.3%)
2001–2002	58	15 (25.9%)	4 (6.9%)	6 (10.3%)	2 (3.4 %)	3 (5.2%)
2003–2005	62	16 (25.8%)	3 (4.8%)	4 (6.5%)	6 (9.7%)	3 (4.8%)

Acronyms: Ashworth Scale (AS); Cerebral Palsy (CP); Cerebrospinal Fluid (CSF); Gross Motor Function Classification System (GMFCS).

COMPLICATIONS OF INTRATHECAL BACLOFEN PUMP THERAPY IN PEDIATRIC PATIENTS [95]

Borowski A, Littleton AG, Borkhuu B et al. *J Pediatr Ortho.* 2010;30(1):76-81.

OBJECTIVE

A U.S. single-center retrospective study and telephone questionnaire assessed complications and parent/caregiver satisfaction of ITB therapy. The series included 174 pediatric patients with spastic CP who were implanted between 1997 and 2006. The mean age at implant was 12 years and 2 months, and mean follow-up was 3 years and 2 months. Fifty-seven patients (32.7%) had a therapy-related complication that required surgical intervention.

RESULTS

Adverse Events: Of all surgical procedures (N=316), 12.3% were associated with device-related complications (n=39). Catheter-related complications (catheter break, disconnection, and malfunction) accounted for the majority (41%) of all complications requiring surgical intervention. All catheter-related complications were resolved with catheter replacement, and no patient had more than 1 catheter-related problem.

The second most frequent complication was infection at the surgical site (9.5% of all complications). Eleven patients developed an acute infection within 60 days of an ITB operation, and 5 patients developed a late infection.

Medical complications not requiring surgical intervention were separately evaluated in 24 new pump implants over one year. The most common medical complications were constipation (n=11, 45.8%), acute urinary retention (n=4, 16.7%), new-onset seizure activity (n=2), decreased trunk control (n=2), new headaches (n=2), increased gastrointestinal reflux (n=2), and increased drooling (n=1).

KEY CONCLUSIONS

Fifty-seven of 174 patients (32.7%) required surgery to resolve a complication. Catheter-related complications were relatively frequent in children with ITB therapy, and were resolved with catheter replacement. The risk/benefit ratio was positive for ITB therapy despite the complications, as 81% of parents/caregivers were satisfied with ITB therapy and 87% would recommend it to others.

SURGICAL PROCEDURES

Reason for Surgical Procedure	No. of Surgical Procedures (N=316)	No. of Patients (N=174)
Primary pump implant	161 (50.9%)	-
Planned device replacement	77 (47.8%)	-
Battery end-of-life	46/77 (59.7%)	-
Catheter replacement for PSF	26/77 (33.8%)	-
Reinsertion after initial explant for infection	5/77 (6.5%)	-
Complication	78 (24.7%)	57 (32.7%)
Infection-Related	30/78 (9.5%) *Infection at pump n=23, infection in back n=7*	16/57 (9.2%)
Other	9/78 (11.5%) *Lack of response n=4, skin irritation with wound dehiscence n=4, significant side effect n=1*	9/57 (15.8%)
Device-Related:	39/78 (50.0%)	38/57 (66.7%)
Catheter	32/78 (41.0%) *Catheter malfunction n=16, catheter break n=9, catheter disconnection n=7*	32/57 (56.1%)
Pump	7/78 (9.0%) *Acute pump failure n=4, pump hypermobility n=3*	6/57 (10.5%)

Acronyms: Cerebral Palsy (CP); Posterior Spinal Fusion (PSF).

BACLOFEN PUMP IMPLANTATION AND SPINAL FUSION IN CHILDREN: TECHNIQUES AND COMPLICATIONS [96]

Borowski A, Shah SA, Littleton AG et al. *Spine.* 2008; 33(18):1995-2000.

OBJECTIVE

A retrospective medical chart and radiographic review compared complications of ITB therapy and posterior spine fusion (PSF) in 62 patients. All patients had severe spasticity due to CP and were treated with ITB therapy between 1997 and 2006. The patients were placed into 4 groups for comparative evaluation. Patients with scoliosis received PSF prior to (n=26), at the same time (n=11), or after (n=25) ITB pump implant. A control group did not have spinal deformity requiring surgical spine intervention, and received only ITB therapy.

RESULTS

Adverse Events: There was no significant difference in rate of infection or device complications between the 4 groups. Most device-related complications were due to catheter fractures and disconnections, and were resolved with catheter replacement.

KEY CONCLUSIONS

The timing of PSF and ITB therapy intervention did not affect the rate of infections or device-related complications. There are surgical technique considerations for treating patients with both PSF and ITB therapy which depend on the order of the procedures.

COMPLICATIONS ASSOCIATED WITH ITB THERAPY AND POSTERIOR SPINAL FUSION

Group	Patient Age (mean years ± SD)		Length of Follow-Up (mean years ± SD)		Infections	Device-Related Complications
	PSF	ITB therapy	PSF	ITB therapy		
Group A, n=26 **PSF before ITB therapy**	12.6 ± 4.1	16.2 ± 3.1	4.2 ± 2.5	1.5 ± 1.0	8%	19%
Group B, n=11 **PSF and ITB therapy concurrently**	11.9 ± 4.0		3.0 ± 2.4		9%	27%
Group C, n=25 **PSF after ITB therapy**	15.1 ± 3.3	10.9 ± 4.5	1.7 ± 1.2	4.5 ± 2.3	8%	16%
Group D, n=103 (control) **ITB therapy alone**	-	11.4 ± 4.8	-	3.3 ± 2.5	9%	26%

Acronyms: Cerebral Palsy (CP); Posterior Spine Fusion (PSF); Standard Deviation (SD).

COMPLICATIONS OF INTRATHECAL BACLOFEN PUMPS IN CHILDREN: EXPERIENCE FROM A TERTIARY CARE CENTER [100]

Ghosh D, Mainali G, Khera J, Luciano M. *Pediatr Neurosurg.* 2013;49(3):138-144.

OBJECTIVE

A retrospective single center chart review evaluated long-term complications of ITB therapy in children. From 1996-2011, 119 patients with spastic CP (n=113) or dystonia* (n=6) were trialed, implanted, and followed for a mean 38 months.

RESULTS

Adverse Events: Major complications occurred in 49 patients. The overall complication-free patient survival at 72 months was 40%. Mechanical complications occurred in 19.3% of patients. Infections occurred in 22% of patients. Fifty percent of infections occurred within the first month following pump placement. Five patients were explanted due to loss of therapeutic efficacy.

Catheter-related complications occurred throughout follow-up with 10 of the 23 complications occurring 3–6 months after starting ITB therapy. Age, sex, weight, pump or catheter tip location, severity of spasticity, and GMFCS score did not predict the occurrence of complications.

KEY CONCLUSIONS

Mechanical (catheter-related) and infection-related complications were the most frequently reported. Infections occurred most commonly within the first month after surgery. Catheter-related complications occurred throughout the follow-up period, with some clustering 3-6 months after implant.

MAJOR COMPLICATIONS OCCURRING WITH ITB THERAPY

Complication Type	No. of Patients
Infection of incision site	19
Catheter displacement/disconnection	10
Skin erosion over pump	8
Catheter fracture	4
Meningitis without infection at incision site	4
Meningitis with infection at incision site	3
CSF leak	1
Total	49

** ITB therapy is not approved for the treatment of dystonia associated with CP.*

Acronyms: Cerebral Palsy (CP); Cerebrospinal Fluid (CSF); Gross Motor Function Classification System (GMFCS).

LONG-TERM CONTINUOUSLY INFUSED INTRATHECAL BACLOFEN FOR SPASTIC-DYSTONIC HYPERTONIA* IN TRAUMATIC BRAIN INJURY: 1-YEAR EXPERIENCE [106]

Meythaler JM, Guin-Renfroe S, Grabb P, Hadley MN. *Arch Phys Med Rehabil.* 1999;80(1):13-19.

OBJECTIVE

This prospective case control study evaluated ITB therapy for severe spasticity in 17 patients with TBI (mean age 25 years, range 10-55 years). Patients were evaluated prior to starting ITB therapy and at 1, 3, 6, and 9 months and 1-year follow-up. Outcomes were spasticity severity (AS), spasm frequency (PSFS), deep tendon reflexes for upper and lower extremities on a scale of 0 to 5, dosing trends, and complications.

RESULTS

Spasticity Outcomes: Patients were titrated over the first 6 months, with observed significant decreases in spasticity, spasm frequency, and reflex scores. Improvement was maintained through 1 year.

At one year, lower extremity spasticity severity (AS) significantly decreased from mean 3.5 to 1.7 points ($P < 0.0001$). Lower extremity spasm frequency (PSFS) significantly decreased from mean 1.8 to 0.2 points ($P < 0.0001$). There was also a significant decrease in average reflex score for the lower extremities from mean 2.5 to 0.1 points ($P < 0.0001$).

Upper extremity responses were similar to lower extremity responses, but of slightly lesser magnitude due to lower initial baseline scores. Upper extremity spasticity severity (AS) significantly decreased from mean 2.9 to 1.6 ($P < 0.0001$). Upper extremity spasm frequency (PSFS) decreased from mean 1.2 to 0.2 ($P < 0.0001$). Biceps reflex score decreased from 2.2 to 1.0 ($P < 0.0001$).

Dosing: Average dose at 1 year was 301 mcg/day (range 120 to 675 mcg/day).

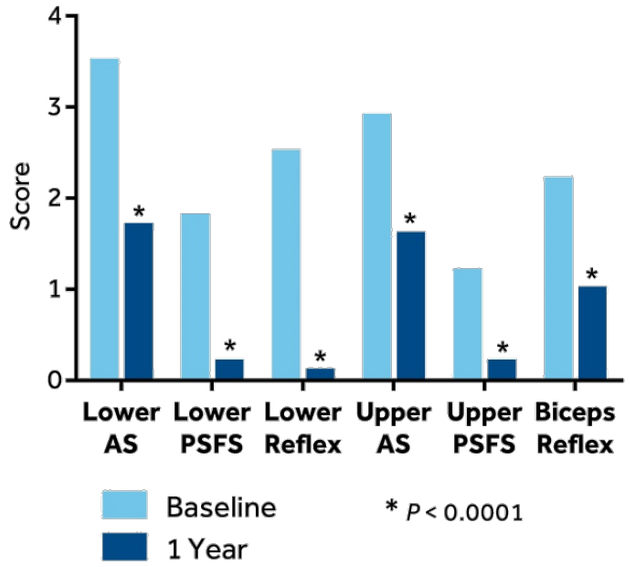
Adverse Events: One patient with a ventriculoperitoneal shunt experienced drowsiness after a 20% ITB dose increase two weeks after pump placement, which resolved with dose decrease. One patient experienced mild postoperative headache which resolved within two days. No other complications were reported.

KEY CONCLUSIONS

ITB therapy is an effective treatment for upper and lower severe spasticity due to TBI.

Limitations: This study had a small number of patients. Four of the patients also received extensive physical therapy and casting/splinting.

MEAN SCORES



** ITB therapy is only approved for the treatment of severe spasticity in patients with mixed movement disorders.*

Acronyms: Ashworth Scale (AS); Penn Spasm Frequency Scale (PSFS); Traumatic Brain Injury (TBI).

PROSPECTIVE ASSESSMENT OF CONTINUOUS INTRATHECAL INFUSION OF BACLOFEN FOR SPASTICITY CAUSED BY ACQUIRED BRAIN INJURY: A PRELIMINARY REPORT [107]

Meythaler JM, McCary A, Hadley MN. *J Neurosurg.* 1997;87(3):415-419.

OBJECTIVE

A prospective study evaluated 3-month ITB therapy outcomes in 12 patients (mean age 28 years, range 17-39 years) with severe spasticity due to acquired brain injury. Nine patients had TBI and 3 had anoxic brain injury. Outcome measures were spasticity severity (AS), spasm frequency (PSFS), and deep tendon reflexes for upper and lower extremities on a scale of 0 to 5.

RESULTS

Spasticity Outcomes: At 3 months, lower extremity spasticity severity (AS) significantly decreased from mean 3.5 to 2.2 points ($P < 0.0001$). Lower extremity spasm frequency (PSFS) significantly decreased from mean 1.8 to 0.2 points ($P < 0.0001$). There was also a significant decrease in average reflex score for the lower extremities from mean 2.7 to 0.2 points ($P < 0.0001$).

Upper extremity responses were similar to lower extremity responses, but of slightly lesser magnitude due to lower initial baseline scores. Upper extremity spasticity severity (AS) significantly decreased from mean 3.3 to 1.9 ($P = 0.0033$). Upper extremity spasm frequency (PSFS) decreased from mean 1.8 to 0.6 ($P = 0.0070$). Biceps reflex score decreased from 2.7 to 1.7 ($P = 0.0111$).

Seven patients had clinically significant reductions in joint contractures, and 5 patients had gait and transfer improvements. Two patients progressed from wheelchair dependence to independent walking with supportive devices.

Dosing: Average dose at 3 months was 183.8 mcg/day (range 100 to 412 mcg/day).

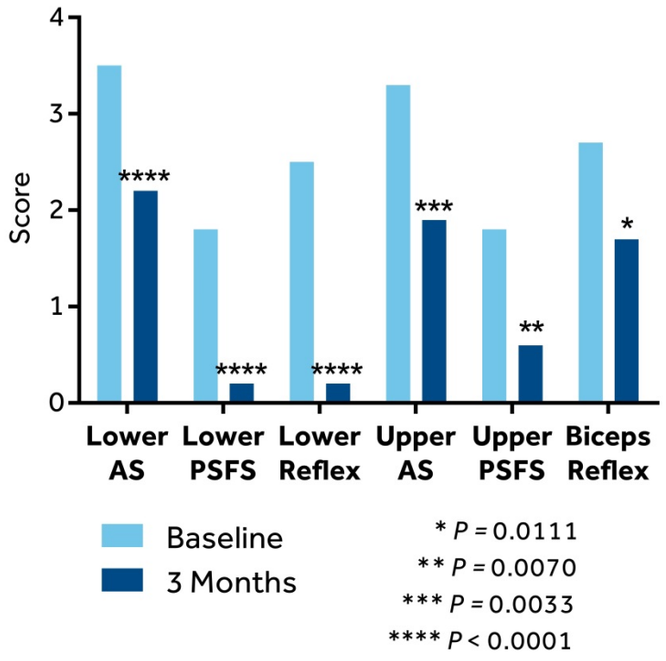
Adverse Events: Reported complications were spinal headache (n=5) that lasted up to 1 week postimplant; postoperative atelectasias (n=3); and Twiddler's syndrome resulting in catheter dislodgement (n=1).

KEY CONCLUSIONS

ITB therapy resulted in significant spasticity improvement.

Limitations: This study had a small number of patients and follow-up was limited to only 3 months of continuous ITB therapy.

MEAN SCORES



Acronyms: Ashworth Scale (AS); Penn Spasm Frequency Scale (PSFS); Traumatic Brain Injury (TBI).

CONTINUOUS INTRATHECAL BACLOFEN INFUSION DELIVERED BY A PROGRAMMABLE PUMP FOR THE TREATMENT OF SEVERE SPASTICITY FOLLOWING TRAUMATIC BRAIN INJURY [111]

Ordia JI, Fischer E, Adamski E, Spatz EL. *Neuromodulation.* 2002 Apr;5(2):103-107.

OBJECTIVE

This prospective observational study evaluated efficacy and safety of ITB therapy in 8 adult patients (mean age 34 years) with severe spasticity due to TBI. Six patients acquired brain injury as a result of an automobile accident and 2 had gun-related wounds. The study first evaluated response to an ITB screening test. Responders were implanted and followed for a mean 5 years. All 8 patients responded to the ITB screening test and went on to pump implant. Spasticity severity was measured using the Ashworth scale.

RESULTS

Spasticity Outcomes: Spasticity (AS) in lower extremities decreased from mean 4.4 to 1.3 ($P < 0.05$), and in upper extremities from mean 2.7 to 1.5 ($P < 0.05$).

Functional Outcomes: Three ambulatory patients reported greater ease of locomotion, and one previously nonambulatory patient could ambulate with the aid of a walker. Caregivers reported that some dependent patients had become easier to care for. Pain was not documented at baseline as a treatment goal, but was reported as improved.

Dosing: The mean initial ITB dose was 146 mcg/day (range 50 to 260 mcg/day). At 6 months, dosage remained steady at 139 mcg/day.

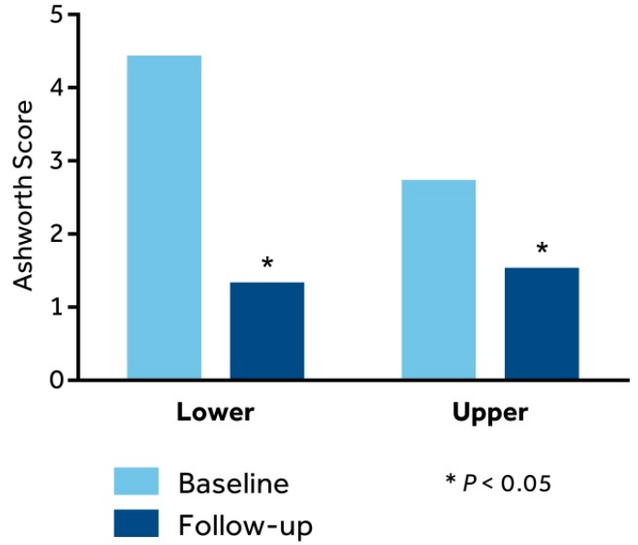
Adverse Events: Two patients experienced muscular hypotonia in the days after continuous ITB therapy was initiated. One patient experienced an areflexic bladder and urinary retention. Erythema over the pump pocket occurred in one patient soon after implant, thought to be an inflammatory response. Another patient's pump was explanted due to pocket site erosion from wheelchair friction. A patient died 3 years postimplant from causes not related to ITB therapy.

KEY CONCLUSIONS

ITB therapy is an effective treatment for properly selected patients with severe spasticity due to traumatic brain injury. In this patient group, there was no evidence that long-term TBI affected response to ITB therapy. Patients had widely varying times from date of injury to pump implant (up to 52 years).

Limitations: This study had a small number of patients and does not well characterize outcomes for function and ease of care.

MEAN ASHWORTH SCORE



Acronyms: Ashworth Scale (AS); Traumatic Brain Injury (TBI).

CONTINUOUS INTRATHECAL BACLOFEN INFUSION IN SEVERE SPASTICITY AFTER TRAUMATIC OR HYPOXIC BRAIN INJURY [94]

Becker R, Alberti O, Bauer BL. *J Neurol.* 1997;244(3):160–166.

OBJECTIVE

A prospective study followed 18 patients (mean age 41 years, range 25-70 years) with traumatic (n=9) or hypoxic (n=9) brain injury treated with ITB therapy. Many patients were severely disabled or in a vegetative state. Therapeutic goals for ITB therapy were improvement in ease of nursing and physiotherapy, and reduction in spasticity-related pain. The follow-up period ranged from 13 to 54 months. Outcomes were spasticity severity (AS), spasm frequency (PSFS), and dosing trends.

RESULTS

Spasticity Outcomes: Mean AS score decreased from 4.5 to 2.33 at last follow-up. Mean PSFS score decreased from 2.16 to 0.94. Outcomes were not analyzed for statistical significance.

Therapeutic Goal Outcomes: The reduction in spasticity facilitated greater ease in limb movement. All patients achieved therapeutic goals for improved nursing, physiotherapy, and spasticity-related pain.

Eight of 12 bedridden patients could be temporarily mobilized in wheelchairs, 3 patients were able to begin mobilizing in bed, and 1 patient had no change in mobilization. Six patients were partially mobile prior to ITB therapy; 3 patients improved their mobility, 1 had no change, and 2 did not have follow-up assessments. In some patients, fixed limb contractures hindered mobilization and physiotherapy even with ITB administration. The authors noted a reduction in signs of pain in these patients.

Eleven patients were admitted with decubitus ulcers. Ulcers completely healed in 5 patients and improved in 5 patients.

Dosing: At last follow-up, mean ITB dose was 265 mcg/day (range 100 to 600 mcg/day).

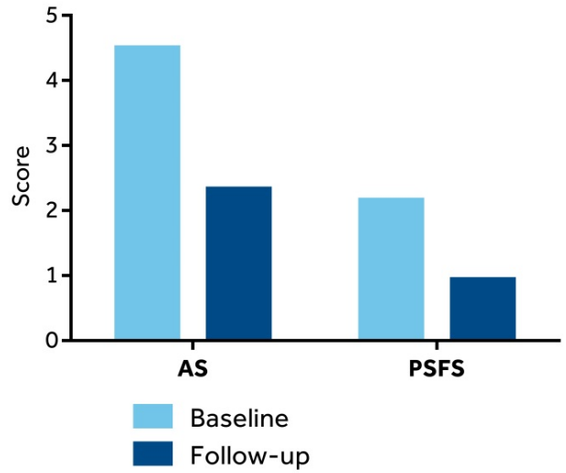
Adverse Events: One patient developed necrosis of a toe which required amputation. Pocket site infection occurred in 1 patient resulting in system explant. Catheter migration occurred in 1 patient, which resolved with revision surgery. An epileptic seizure occurred in 1 patient during the ITB screening test. No further seizures were reported in the patient with long-term ITB therapy.

KEY CONCLUSIONS

Ease of nursing, physiotherapy, and signs of spasticity-related pain improved with ITB therapy in a small group of severely disabled patients with brain injury.

Limitations: Function and pain were not easily assessed in this patient group. The authors assumed pain was present when patients made pain-associated gestures and facial movements. There was no assessment of statistical significance.

MEAN SPASTICITY SCORE



** Some patients were implanted less than one year after their injury. ITB therapy is not approved for the treatment of severe spasticity less than one year post-traumatic brain injury. The labeled 1-year wait applies only to patients with brain injury due to trauma.*

Acronyms: Ashworth Scale (AS); Penn Spasm Frequency Scale (PSFS); Traumatic Brain Injury (TBI).

TREATMENT OF CEREBRAL ORIGIN SPASTICITY WITH CONTINUOUS INTRATHECAL BACLOFEN DELIVERED VIA AN IMPLANTABLE PUMP: LONG-TERM FOLLOW-UP REVIEW OF 18 PATIENTS [113]

Rawicki B. *J Neurosurg.* 1999;91(5):733-736.

OBJECTIVE

A prospective long-term study assessed outcomes in 18 patients treated with ITB therapy for severe spasticity of cerebral origin due to BI (n=12), CP (n=3), stroke (n=2), or other (n=1). Follow-up ranged from 12 months to 9 years. Outcome measures were spasticity severity (MAS), spasm frequency (PSFS), patient transfers (FIM transfer score), and hygiene (Snow Hygiene Score; ability to clean and catheterize).

RESULTS

Outcomes in Total Group:

- At last follow-up, significant improvements were observed in spasticity severity ($P < 0.001$), spasm frequency ($P < 0.002$), transfers ($P < 0.002$), and hygiene ($P < 0.001$).

Nursing Care Sub-Group Outcomes:

- Eight patients were selected for ITB therapy with the primary goal to improve nursing care. These patients demonstrated significant improvement in spasticity ($P < 0.001$), spasms ($P < 0.038$), and hygiene ($P < 0.001$). There was no significant improvement in transfers.

Function Sub-Group Outcomes:

- Ten patients were selected for ITB therapy with the primary goal to improve function. These patients demonstrated significant improvement in spasticity ($P < 0.01$) and spasms ($P < 0.015$). Eight of 10 patients were dependent during transfers and had a significant decrease in burden of transfer ($P < 0.001$).

Dosing: Mean ITB dose at last follow-up was 350 mcg/day (range 80 to 900 mcg/day).

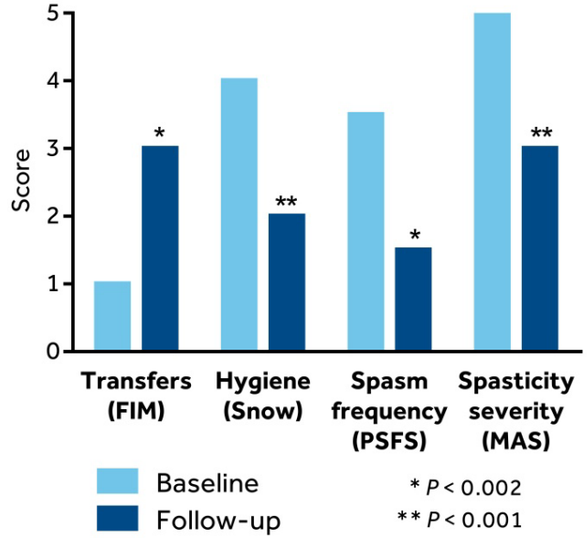
Adverse Events: Complications were: early postimplant infection at the pump pocket site successfully treated with antibiotics (n=1); seroma at the pump pocket site (n=1); ITB overdose due to a programming error with a dose change (n=1) and due to an inadvertent bolus during catheter troubleshooting (n=1), with no permanent sequelae; kinked catheter replacement (n=1, 2 replacements); and hypothermia with ITB doses above 300 mcg/day. Three patient deaths occurred due to respiratory infection or failure and disease progression; ITB therapy was not implicated in the deaths.

KEY CONCLUSIONS

ITB therapy improved spasticity severity and frequency, hygiene, and transfers in patients with severe spasticity of cerebral origin who did not respond to conventional medical management.

Limitations: This study had a small number of patients with varying follow-up durations. Although patients were selected for ITB therapy to improve function and nursing care, the authors did not specifically describe improvement in these goals. Rather, they reported outcomes in spasticity, hygiene, and patients which may affect function and level of nursing care. The Snow Hygiene Score is not validated for cerebral origin spasticity and is not commonly used.

MEAN SCORES, TOTAL GROUP



Acronyms: Brain Injury (BI); Cerebral Palsy (CP); Functional Independence Measure (FIM); Modified Ashworth Scale (MAS); Penn Spasm Frequency Scale (PSFS).

LONG-TERM INTRATHECAL BACLOFEN INFUSION IN SUPRASPINAL SPASTICITY OF ADULTHOOD [98]

Dario A, Di Stefano MG, Grossi A et al. *Acta Neurol Scand.* 2002;105(2):83-87.

OBJECTIVE

A prospective study was conducted to assess long-term efficacy and safety of ITB therapy in 14 patients (10 males, 4 females; mean age 38.8 years, range 18-56 years) with severe spasticity due to brain injury (6 TBI, 8 other BI). Follow-up averaged 23.5 months (range 6-65 months). At baseline, 8 patients had a GOS score of 2 (vegetative state) and 6 had a GOS score of 3 (severe disability). Outcomes included spasticity severity (AS), spasm frequency (SFS), and complications.

RESULTS

Spasticity Outcomes: Spasticity severity (AS) in the upper and lower extremities improved significantly at the most recent follow-up visit compared to baseline ($P < 0.05$). Spasm frequency (SFS) also decreased significantly ($P < 0.001$).

Functional Outcomes: GOS scores remained unchanged in 12 patients and improved in 2 patients. One patient improved from a GOS score of 2 (vegetative state) to 3 (severe disability), and another patient improved from a GOS score of 3 to 4 (moderate disability).

Dosing: The mean ITB dose was 305 mcg/day (range 90 to 510 mcg/day).

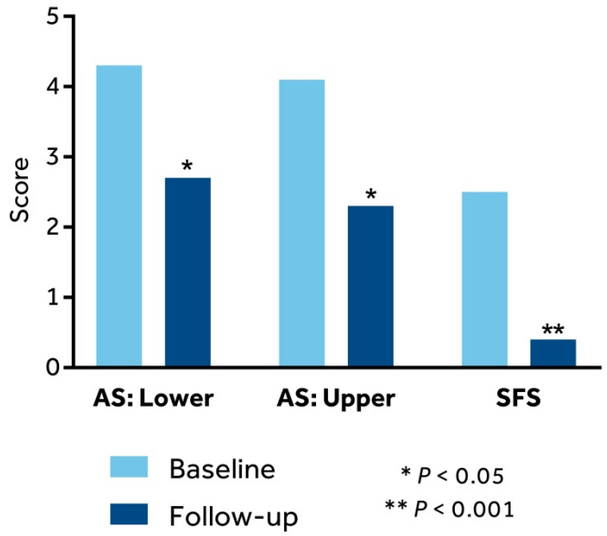
Adverse Events: One superficial wound erosion was reported. There were no side effects of ITB administration.

KEY CONCLUSIONS

Improvements in spasticity outcomes were observed in patients with severe spasticity due to brain injury.

Limitations: No control group was included in the study.

MEAN SPASTICITY SCORES



Acronyms: Ashworth Scale (AS); Brain Injury (BI); Glasgow Outcomes Scale (GOS); Spasm Frequency Scale (SFS); Traumatic Brain Injury (TBI).

INTRATHECAL BACLOFEN MANAGEMENT OF POSTSTROKE SPASTIC HYPERTONIA: IMPLICATIONS FOR FUNCTION AND QUALITY OF LIFE [103]

Ivanhoe CB, Francisco GE, McGuire JR et al. *Arch Phys Med Rehabil.* 2006;87(11):1509-1515.

OBJECTIVE

A prospective long-term study evaluated functional and quality of life outcomes for 74 patients with severe poststroke spasticity treated with ITB therapy. Of 94 patients recruited, 93 were enrolled and received an ITB screening test, 91 responded positively to the screening test, and 74 were implanted. The mean age for all recruited patients was 57.2 years (range 23.7-81.9 years), and mean time from stroke to enrollment was 3.3 years (range 0.1-25.2 years).

Outcome measures for ITB therapy were function (FIM), quality of life (SIP), spasticity (AS), muscle strength (MMT), dosing trends, and frequency and severity of adverse events. Patients were evaluated prior to starting ITB therapy and at 3 and 12 months postimplant. Data for 72 patients was available at 3 month follow-up and for 57 patients at 12 month follow-up.

RESULTS

Spasticity and Motor Strength Outcomes: Mean combined upper and lower extremity AS scores improved significantly at 3 and 12 months ($P < 0.001$). Individual upper extremity and lower extremity scores for the affected side improved significantly at both time points ($P < 0.001$). Muscle strength scores were not significantly different with ITB therapy, demonstrating that the unaffected side was not weakened.

Functional Outcomes: There was significant improvement in overall FIM scores at 3 months ($P = 0.001$) and 12 months ($P = 0.017$). Motor subscores were significantly improved at 3 months ($P = 0.002$) and 12 months ($P = 0.026$). Transfers and self-care subscores were significantly improved only at 3 months ($P = 0.017$ and $P = 0.003$, respectively). There was no significant improvement in FIM subscores for sphincter control, locomotion, cognitive, communication, or social cognition.

Quality of Life Outcomes: Mean total SIP score significantly improved at 12 months ($P < 0.001$). Improvements were significant for the physical and psychosocial domains (both $P < 0.001$). SIP categories for sleep/rest and recreation/pastimes were significantly improved with ITB therapy ($P = 0.041$ and $P = 0.035$, respectively).

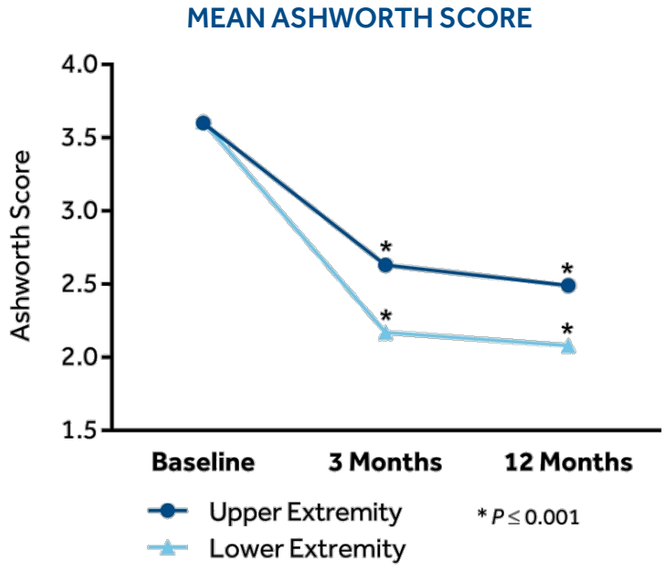
Dosing: Mean ITB dose was 161.2 mcg/day at 3 months and 287.4 mcg/day at 12 months. Most patients were treated with simple continuous infusion.

Adverse Events: Adverse events during long-term ITB therapy with >5% frequency were reported and included: accidental injury (n=12, mostly falls), somnolence (n=9), dizziness (n=8), hypotonia (n=8), headache (n=4), constipation (n=4), pain (n=5), urinary tract infection (n=4), hypertonia (n=4), spinal headache (n=6), CSF leak (n=4), and catheter complication, not specified (n=8). There were 3 deaths during the study, none of which were drug or device-related.

KEY CONCLUSIONS

ITB therapy improved spasticity, function for activities of daily living, and quality of life in adult patients with severe spasticity due to stroke. Positive outcomes were seen through 12 months of therapy.

Limitations: This study was not blinded and did not have a control group. Interrater reliability was not assessed for the outcome measures. This study did not adequately account for motor control and strength that may have been unmasked with decreased spasticity. Variables that may have affected results include time from stroke, baseline severity and function, catheter tip vertebral level placement, and physical therapy and other medications.



Acronyms: Ashworth Scale (AS); Cerebrospinal Fluid (CSF); Functional Independence Measure (FIM); Manual Muscle Test (MMT); Sickness Impact Profile (SIP).

PROSPECTIVE 12-MONTH STUDY OF INTRATHECAL BACLOFEN THERAPY FOR POSTSTROKE SPASTIC UPPER AND LOWER EXTREMITY MOTOR CONTROL AND FUNCTIONAL IMPROVEMENT [114]

Schiess MC, Oh IJ, Stimming EF et al. *Neuromodulation.* 2011;14(1):38-45.

OBJECTIVE

A prospective observational study assessed 12-month outcomes of ITB therapy for 26 adult patients with severe spasticity due to stroke. Of 45 patients who received an ITB screening test, 33 responded positively to the screening test, 30 were implanted, and 26 had 12 month follow-up data. The mean age for implanted patients was 52 years (range 27-75 years) and mean time from stroke to enrollment was 6.4 years (range 1-50 years).
Clinical measures were selected for assessment of tone and functional motor outcomes and included spasticity (MAS), muscle strength (MMT), function (FIM), spasticity-related pain (VAS), quality of life (SSQL), upper extremity function (MAL), and gait (distance and velocity). Patients were evaluated at baseline and 3, 6, and 12 months. Gait assessment was conducted at baseline and 12 months. Complications were not reported.

RESULTS

Spasticity and Motor Strength Outcomes: Mean lower extremity MAS score significantly decreased ($P \leq 0.001$) and mean lower extremity MMT score significantly increased ($P \leq 0.0001$). Mean upper extremity MAS score significantly decreased ($P \leq 0.01$) and mean upper extremity MMT score significantly increased ($P \leq 0.05$). Spasticity-related pain (VAS) ranged from 0 to 8 at baseline, with 11 patients rating pain at 0. At 12 months, VAS ranged from 0 to 7 with 14 patients rating pain at 0.

Functional Outcomes: Significant improvements were observed at 12 months in FIM scores for transfers, grooming, eating, bathing, toileting, and ambulation ($P < 0.05$) and for dressing-upper body and gait distance ($P < 0.01$). There was no significant change in FIM scores for bed mobility and dressing-lower body. MAL significantly improved in gross and fine motor activities for amount of use and quality of movement in performing common activities of daily living (all scores $P \leq 0.007$).

Quality of Life Outcomes: A patient survey showed significant 12-month improvement in SSQL domains for family roles, mobility, social roles, thinking, upper extremity function, and work/productivity ($P \leq 0.05$); personality ($P \leq 0.006$); and self-care ($P \leq 0.001$). There was no significant change in energy, language, mood, or vision domains.

Gait Outcomes: Gait performance improved with ITB therapy. Velocity significantly improved from 0.55 m/second at baseline to 0.77 m/second at 12 months ($P \leq 0.05$). Distance in a 6 minute walk improved from 558 feet to 746 feet ($P \leq 0.05$). The gait analysis excluded 3 nonambulatory patients.

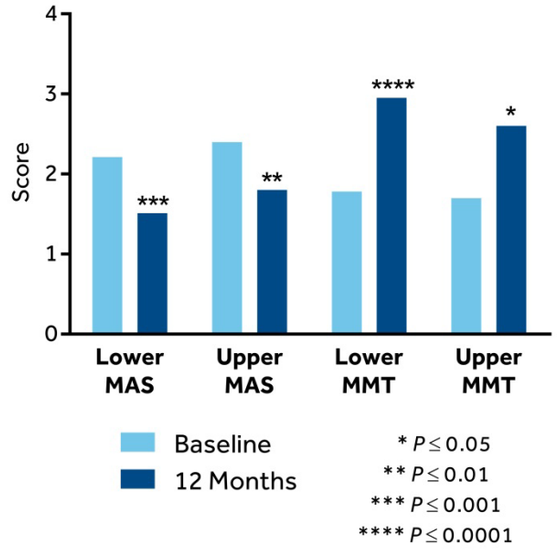
Dosing: Six patients received continuous infusion of mean 440 mcg/day (range 135 to 2118 mcg/day). Twenty patients received periodic bolus infusion of mean 543 mcg/day (range 211 to 1994 mcg/day). The mean basal rate was 4.6 mcg/hour and mean bolus dose was 105 mcg (range 30 to 476 mcg/day) every 6 hours. Patients were converted from continuous to periodic bolus infusion when they demonstrated a loss of efficacy and when total daily dose reached 200 to 300 mcg. All patients reached optimum dosing by 6 months.

KEY CONCLUSIONS

Patients with poststroke spastic hemiparesis can benefit from ITB therapy. Spastic tone was reduced, motor strength was increased, and gait was improved. Clinically significant improvements in functional independence and quality of life were reported.

Limitations: Variables that were not accounted for and that may have affected results include time from stroke and baseline severity and function.

MEAN SCORES



Acronyms: Functional Independence Measure (FIM); Manual Muscle Test (MMT); Modified Ashworth Scale (MAS); Motor Activity Log (MAL); Sickness Impact Profile (SIP); Stroke-Specific Quality of Life (SSQL); Visual Analog Scale (VAS).

INTRATHECAL BACLOFEN FOR SPASTIC HYPERTONIA FROM STROKE [105]

Meythaler JM, Guin-Renfroe S, Brunner RC, Hadley MN. *Stroke*. 2001;32(9):2009-2109.

OBJECTIVE

An observational prospective study evaluated efficacy and safety of ITB therapy in patients with severe spastic hypertonia due to stroke. Twenty-one patients were screened with ITB in a randomized, double-blind placebo-controlled, cross-over screening test of either baclofen or saline. Mean age of screened patients was 53 years (range 16-86 years). Nineteen patients were implanted; 2 were dropped from analysis due to potentially confounding factors, 4 were followed up to 6 months, and 13 were followed up to 12 months. Mean time after stroke onset to implant was 41 months (range 10-107 months).
Outcome measures were spasticity severity (AS), spasm frequency (PSFS), deep tendon reflexes for upper and lower extremities on a scale of 0 to 5, dosing trends, and adverse events.

RESULTS

Spasticity Outcomes: Lower extremity spasticity severity (AS) significantly decreased from mean 3.7 to 1.8 points ($P < 0.0001$). There was not a significant decrease in lower extremity spasm frequency (PSFS). Average reflex score for the lower extremities decreased from mean 2.4 to 1.0 points ($P < 0.0001$).

Upper extremity responses were similar to lower extremity responses, but of slightly lesser magnitude due to lower initial baseline scores. Upper extremity spasticity severity (AS) significantly decreased from mean 3.2 to 1.8 ($P < 0.0001$). There was not a significant decrease in upper extremity spasm frequency (PSFS) or the biceps reflex score.

Functional Outcomes: Three patients progressed from wheelchair dependence to independent walking with supportive devices. All dependent patients were reportedly more comfortable and easier to manage with regard to activities of daily living. No patient reported reduction in motor strength.

Dosing: Average dose at 1 year was 268 mcg/day (range 50 to 660 mcg/day). Dose adjustments were rather frequent in the first few months of ITB therapy in order to adapt to changes in lifestyle and functional status.

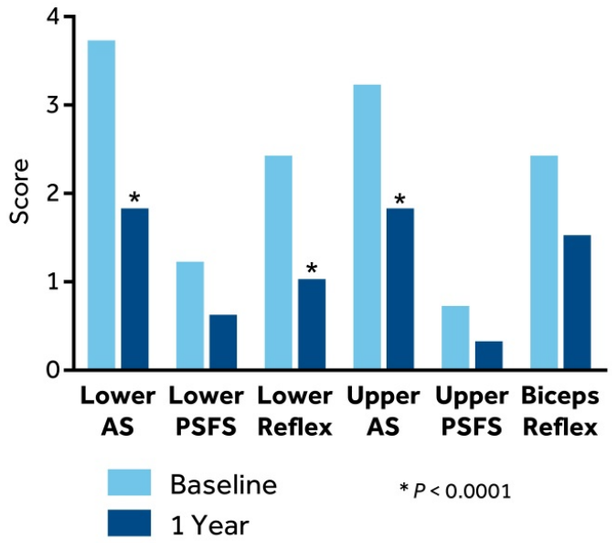
Adverse Events: Two patients reported headache during the screening test. Postimplant headaches potentially due to CSF leak were reported in several patients. With ITB therapy, 5 patients experienced urinary retention, which resolved with dosage changes, and 1 patient required a catheter revision.

KEY CONCLUSIONS

ITB therapy can maintain a reduction in stroke-related upper and lower extremity spasticity.

Limitations: Selected and screened patients had greater lower extremity spasticity than upper, thus ITB therapy's effect on upper extremity severe spasticity is not well characterized in this study.

MEAN SCORES



Acronyms: Ashworth Scale (AS); Cerebrospinal Fluid (CSF); Penn Spasm Frequency Scale (PSFS).

IMPROVEMENT IN WALKING SPEED IN POSTSTROKE SPASTIC HEMIPLEGIA AFTER INTRATHECAL BACLOFEN THERAPY: A PRELIMINARY STUDY [99]

Francisco GE, Boake C. *Arch Phys Med Rehabil.* 2003;84(8):1194-1199.

OBJECTIVE

A prospective case series evaluated walking function in 10 adults with poststroke spasticity treated with ITB therapy. Mean age was 51.7 years (range 31-69 years) and patients were mean 28.6 months (range 9-55 months) from stroke onset to pump implant. Patients were followed for a mean 8.9 months after implant. Patients also received physical therapy once spasticity was optimally managed with ITB therapy.

Outcome measures were customary walking speed (time to walk 50 feet), functional walking category (based on observation of ambulation and walking-speed test), functional mobility (locomotion-walking and stairs items of FIM, community access item of the FAM, and unpublished Sit-to-Stand and Stand-to-Sit), and lower extremity spasticity severity (MAS).

RESULTS

Walking Speed Outcomes: In 8 unassisted ambulatory patients there was a significant increase in walking speed ($P < 0.05$). Of 2 patients that required assistance before ITB therapy, one patient no longer required assistance at follow-up and the other patient reduced their level of assistance from maximal to minimal.

Functional Walking Outcomes: Three patients improved their functional walking category at the follow up (most-limited community walker to community walker; limited household walker to unlimited household walker; and physiologic walker to limited household walker). The remaining 7 patients had no change in their functional walking category.

Functional Mobility Outcomes: Mean functional mobility score improved significantly in 6 patients ($P = 0.0277$) with a large effect size.

Spasticity Outcomes: Mean lower extremity spasticity (MAS) was significantly improved in all 10 patients ($P = 0.0051$) with a large effect size. Unaffected limbs maintained tone and strength.

Adverse Events: Headache, nausea, vomiting, excessive weakness, and transient urinary retention were each reported by 2 patients. Another patient had urinary retention, was found to have flaccid bladder, and received suprapubic tube placement.

KEY CONCLUSIONS

ITB therapy, in combination with physical therapy, facilitated improved in walking function in patients with poststroke spasticity.

Limitations: Small patient number limits the statistical power of this study and the inferences that can be drawn between improvement in spasticity and improvement in walking speed. Additionally, because all participants received both ITB therapy and physical therapy, any improvements due to ITB are confounded with physical therapy.

MAIN OUTCOME MEASURES

	Mean ± SD	
	Baseline	Follow-up
Walking Speed (cm/s)	36.6 ± 29.4	52.0 ± 37.6 *
Lower Extremity MAS	2.1 ± 0.6	0.4 ± 0.3 *
Functional Mobility Score	18.3 ± 7.0	21.0 ± 6.5 **

** P = 0.0051, large effect size*
*** P = 0.0277, large effect size*

Acronyms: Functional Assessment Measure (FAM); Functional Independence Measure (FIM); Modified Ashworth Scale (MAS); Standard Deviation (SD).

CLINICAL AND SAFETY EVIDENCE: **SPINAL ORIGIN SPASTICITY**

Lead Author	Year	Abbreviated Title	Journal	Page
Spinal Origin				
Vidal J	*2000*	Safety and efficacy of ITB infusion by implantable pump for the treatment of severe spasticity: A Spanish multicenter study	*Neuromodulation*	50
Ordia JI	*1996*	Chronic intrathecal delivery of baclofen by a programmable pump for the treatment of severe spasticity	*J Neurosurg*	51
Coffey JR	*1993*	ITB for intractable spasticity of spinal origin: Results of a long-term multicenter study	*J Neurosurg*	52
Gianino JM	*1998*	Quality of life: Effect of reduced spasticity from ITB	*J Neurosci Nurs*	53
Azouvi P	*1996*	ITB administration for control of severe spasticity: Functional improvement and long-term follow-up	*Arch Phys Med Rehabil*	54
Guglielmino A	*2006*	Continuous ITB administration by a fully implantable electronic pump for severe spasticity treatment: our experience	*Minerva Anestesiol*	55
Ordia JI	*2002*	Continuous ITB infusion by a programmable pump in 131 consecutive patients with severe spasticity of spinal origin	*Neuromodulation*	56
Spinal Origin				
Zahavi A	*2004*	Long term effect (more than five years) of ITB on impairment, disability, and quality of life in patients with severe spasticity of spinal origin	*J Neurol Neurosurg Psychiatry*	57
Middel B	*1997*	Effect of ITB delivered by an implanted programmable pump on health related quality of life in patients with severe spasticity	*J Neurol Neurosurg Psychiatry*	58
Dario A	*2001*	Functional improvement in patients with severe spinal spasticity treated with chronic ITB infusion	*Funct Neurol*	59
Draulans N	*2013*	ITB in multiple sclerosis and spinal cord injury: complications and long-term dosage evolution	*Clin Rehabil*	60
Multiple Sclerosis				
Vender JR	*2006*	ITB therapy and multiple sclerosis: outcomes and patient satisfaction	*Neurosurg Focus*	61
Khan AA	*2010*	Clinical outcome and complications of ITB pump in multiple sclerosis patients: A retrospective study	*NeuroRehabilitation*	62
Spinal Cord Injury				
For outcomes of ITB therapy for patients with severe spasticity due to spinal cord injury, please refer to publications under the general 'Spinal Origin' category.				

SAFETY AND EFFICACY OF INTRATHECAL BACLOFEN INFUSION BY IMPLANTABLE PUMP FOR THE TREATMENT OF SEVERE SPASTICITY: A SPANISH MULTICENTER STUDY [126]

Vidal J, Fenollosa P, Martin E et al. *Neuromodulation*. 2000;3(4):175-182.

OBJECTIVE

A prospective open-label multicenter study evaluated ITB therapy for 72 patients (mean age 42.2 years, range 17-71 years) with severe spasticity of spinal origin. Sixty-four patients (SCI, n=40; MS, n=5; other cause, n=19) responded to an ITB screening test and were implanted. Outcome measures were spasticity severity (AS), spasm frequency (PSFS), muscular strength (Lovett scale), dosing trends, and functional surveys of self-care, wheelchair status, and spasticity-related pain. Patients were followed for 36 months.

RESULTS

Spasticity Outcomes: Spasticity was significantly improved with ITB therapy. Mean lower extremity AS scores significantly improved by more than 2 points ($P < 0.001$). Mean spasm frequency scores also significantly decreased by more than 2 points ($P < 0.001$). There was no change in muscular strength. A subgroup analysis revealed that patients less than 25 years of age (n=9) had a significantly better reduction in spasticity than patients older than 25 years (n=55) ($P = 0.004$), and that patients with complete lesions (n=29) had a significantly better reduction in spasticity than patients with partial lesions (n=35) ($P = 0.020$).

Functional Outcomes: Investigators evaluated functional outcomes for drinking from a glass, eating, clothing from waist up, clothing from waist down, dressing up, and washing. Overall there was a trend for a reduced number of patients who were totally dependent for these activities of daily living. Transfers from wheelchair to bed or vice versa did not change significantly.

The proportion of patients who experienced moderate discomfort in a wheelchair or needed to be fastened into a wheelchair decreased from 51.8% at baseline to 17.5% at last follow-up. The remaining 82.5% of patients had low or no wheelchair discomfort with ITB therapy.

The proportion of patients with continuous or common spasticity-related pain was reduced from 57.9% at baseline to 23.4% at last follow-up. The remaining 76.6% of patients had uncommon or no spasticity-related pain with ITB therapy.

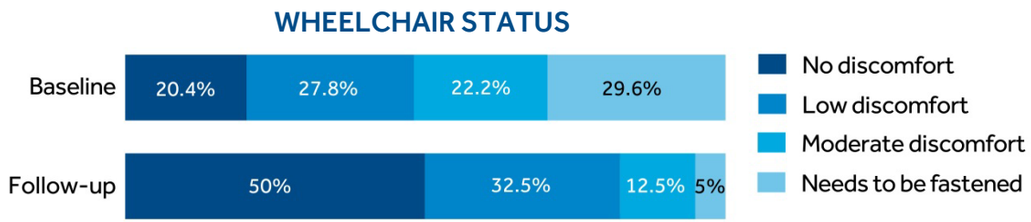
Dosing: Mean initial dose was 83.2 mcg/day (range 25 to 200 mcg/day). Mean dose at last follow-up was 270 mcg/day (range 25 to 800 mcg/day). Most doses stabilized after 6 to 12 months of ITB therapy. There were no dose increases after 12 months.

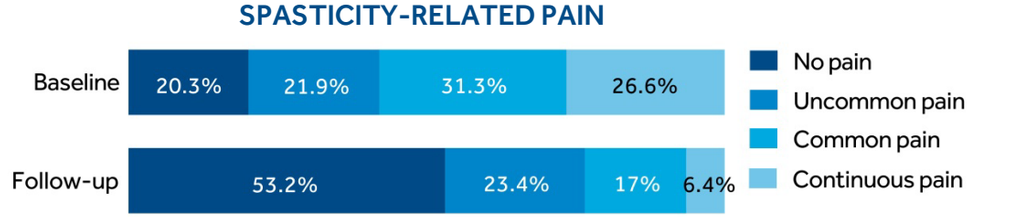
Adverse Events: Reported drug-related adverse events were orthostatic hypertension that resolved with dose reduction (n=3), and generalized pruritus that resolved when ITB infusion was restarted (n=2). System-related adverse events were catheter complications that resolved with catheter revision/replacement (n=14), and system explant due to infection and subsequent reimplant after 6 months (n=1). Two patient deaths occurred due to suicide (n=1) and cardiopulmonary complications (n=1); ITB therapy was not implicated in the deaths.

KEY CONCLUSIONS

ITB therapy improved spasticity, spasticity-related pain, wheelchair status, and activities of daily living for patients with severe spasticity of spinal origin. Dosing was mostly stable by 6 months, with some mild increases observed from 6 to 12 months.

Limitations: Functional outcomes were subjective and not powered for statistical analysis.





Acronyms: Ashworth Scale (AS); Multiple Sclerosis (MS); Penn Spasm Frequency Scale (PSFS); Spinal Cord Injury (SCI).

CHRONIC INTRATHECAL DELIVERY OF BACLOFEN BY A PROGRAMMABLE PUMP FOR THE TREATMENT OF SEVERE SPASTICITY [84]

Ordia JI, Fischer E, Adamski E, Spatz EL. *J Neurosurg*. 1996;85(3):452-457.

OBJECTIVE

This prospective open-label study evaluated efficacy, safety, and medical costs of ITB therapy in 59 patients with severe spinal origin spasticity due to SCI (n=27), MS (n=26), or other cause (n=6). Patient mean age was 42 years (range 16-73 years) and mean duration of symptoms was 12 years (range 5 months-34 years). Patients were followed for a mean of 42 months. Outcome measures included spasticity severity (AS), spasm frequency (PSFS), dosing trends, and patient reports of improved function.

RESULTS

Spasticity Outcomes: Spasticity was significantly improved with ITB therapy. Spasticity severity (AS) decreased from mean 4.3 to 1.4 points at last follow-up ($P < 0.0005$). Spasm frequency (PSFS) decreased from mean 3.6 to 0.5 points at last follow-up ($P < 0.0005$).

Functional Outcomes: ITB therapy improved activities of daily living. Some patients reported easier transfers from wheelchair to bed, as well as improvement in muscle aches, spasticity-related pain, and sleep due to reduced spasticity. One patient reported improved that they were able to discontinue large doses of oral antispasmodics and was more alert. Being more alert helped in achieving improved grades at college. Several females reported greater ease of care for personal hygiene when they no longer had hip adductor spasticity and hip scissoring. Self-catheterization was easier in all patients with bladder dysfunction. Four patients had improved ambulation.

Dosing: Mean initial dose was 126 mcg/day (range 14-280 mcg/day). Most patients reached a stable dose by 6 months. Mean doses with long-term ITB therapy were 256 mcg/day at 6 months, 272 mcg/day at 12 months, 276 mcg/day at 24 months, and 275 mcg/day at 48 months (range 42-700 mcg/day). There were no significant differences between ITB doses for SCI and MS patients, although MS patients had slightly greater variability in dose likely due to fluctuating MS symptoms.

Nonambulatory patients required higher doses than ambulatory patients ($P = 0.03$).

Adverse Events: Drug tolerance occurred in a patient with MS after 21 months of ITB therapy. The patient was treated with a drug holiday and restarted at 100 mcg/day. Preexisting constipation worsened in 6 patients, requiring a change in bowel regimen. Dosages were decreased to resolve hypotonia (n=3), urinary retention (n=3), and nausea, dizziness, and drowsiness (n=1).

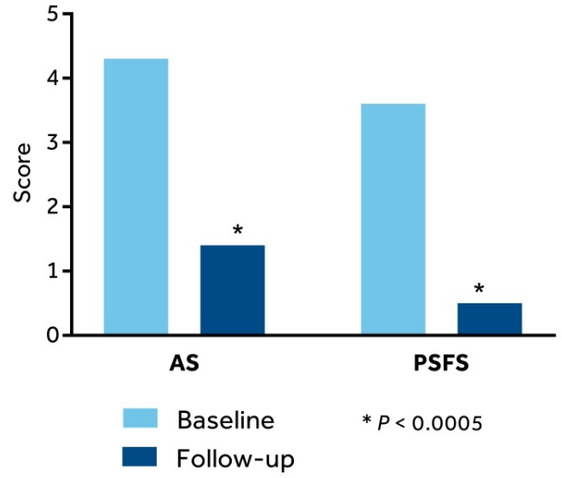
Fifteen patients had 19 catheter problems: breaks (n=7), occlusions (n=9), punctures (n=2), and dislodgement (n=1). Two patients were explanted due to pocket site infection and skin erosion. A CSF leak required laminectomy and dura repair. Two patients died during follow-up, neither due to complications from ITB therapy.

KEY CONCLUSIONS

ITB therapy improved spasticity and activities of daily living for patients with severe spasticity of spinal origin. Dosing was mostly stable by 6 months.

Limitations: Functional outcomes were subjective and not powered for statistical analysis.

MEAN SPASTICITY SCORES



Acronyms: Ashworth Scale (AS); Multiple Sclerosis (MS); Penn Spasm Frequency Scale (PSFS); Spinal Cord Injury (SCI).

INTRATHECAL BACLOFEN FOR INTRACTABLE SPASTICITY OF SPINAL ORIGIN: RESULTS OF A LONG-TERM MULTICENTER STUDY [3]

Coffey JR, Cahill D, Steers W et al. *J Neurosurg*. 1993;78(2):226-232.

OBJECTIVE

A prospective multicenter study evaluated efficacy and safety of ITB therapy for patients with severe spasticity of spinal origin. Fifteen centers in the U.S. participated in the study. The study was conducted in 2 phases. In the first phase, 93 adult patients were screened via a randomized, double-blind placebo-controlled protocol. This controlled clinical trial of ITB screening supported U.S. FDA approval of ITB therapy for severe spinal origin spasticity.

In the second phase, 75 patients (mean age 42.1 years, range 25-69 years) proceeded to pump implant and were followed for mean 19 months. Spasticity etiologies of implanted patients were cervical SCI (n=29), thoracic/lumbar SCI (n=18), MS (n=27), and other (n=1). Outcome measures were spasticity severity (AS), spasm frequency (PSFS), dosing trends, and adverse events.

RESULTS

Spasticity Outcomes: Spasticity was significantly improved with ITB therapy. At last follow-up, spasticity severity (AS) had decreased from 3.9 to 1.7 points. Spasm frequency decreased from 3.1 to 1.0 points. Total group scores were not analyzed for statistical significance. Reductions remained fairly stable over time and did not differ significantly between the MS and SCI patients.

Dosing: Mean initial dose was 187 mcg/day, and increased to mean 405 mcg/day at last follow-up. There was a significant difference in mean daily dose at last follow-up between SCI and MS patients (462 mcg/day and 320 mcg/day, respectively; $P < 0.05$).

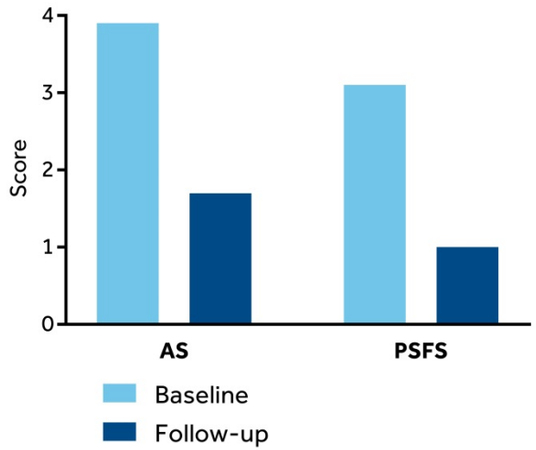
Adverse Events: Long-term therapy drug-related complications occurred in 12% of patients and included respiratory depression (n=1), hypotension (n=2), seizure (n=2), hypertension (n=1), depression (n=2), and drowsiness (n=1). All were resolved with medical management. There were 31 cases of device-related complications requiring a secondary surgical or invasive procedure. These included 22 catheter complications, 3 pump failures, and 6 wound complications. There was 1 subcutaneous drug extravasation during pump refill, 1 pocket seroma, 1 CSF leak, and 1 pump-site discomfort. Three patients died during the study of causes probably unrelated to ITB therapy.

KEY CONCLUSIONS

ITB therapy improved severe spasticity of spinal origin in the long-term with a low incidence of serious drug and device-related complications.

Limitations: Follow-up times ranged from 5 to 41 months. Thus, data for last follow-up may not be fully representative of the long-term experience with ITB therapy.

MEAN SPASTICITY SCORES



Acronyms: Ashworth Scale (AS); Cerebrospinal Fluid (CSF); Multiple Sclerosis (MS); Penn Spasm Frequency Scale (PSFS); Spinal Cord Injury (SCI).

QUALITY OF LIFE: EFFECT OF REDUCED SPASTICITY FROM INTRATHECAL BACLOFEN [120]

Gianino JM, York MM, Paice JA, Shott S. *J Neurosci Nurs*. 1998;30(1):47-54.

OBJECTIVE

ITB therapy's impact on quality of life and spasticity was prospectively studied in 25 adult patients with severe spasticity due to MS (n=15), SCI (n=7), or other causes (n=3). Mean age was 39.4 years (range 21-70 years). Patients were evaluated at baseline and 3, 6, 9, and 12 months follow-up. The primary outcome was quality of life measured using the QLI and SIP tools. The QLI measured quality of life aspects for health and functioning, socioeconomic, psychological/spiritual, and family. The SIP measured quality of life aspects for physical, psychological, and total function. Spasticity severity (AS) and spasm frequency (PSFS) was also measured.

RESULTS

Quality of Life Outcomes at 12 Months: Twelve month data was available for 16 patients. Total SIP significantly improved at 12 months compared to baseline ($P = 0.0042$). Significant improvement was also seen in physical subscale SIP scores ($P = 0.0213$) and psychological subscale SIP scores ($P = 0.0352$). Total SIP scores tended to be higher for patients with quadriparesis than paraparesis, indicating greater function with ITB therapy for patients with paraparesis ($P = 0.048$). There was no significant improvement in total or subscale QLI scores.

A qualitative patient survey reported that ITB therapy improved spasticity, ability to perform activities of daily living, mobility, and spasticity-related pain. Patients reported greater independence and comfort.

Spasticity Outcomes at 12 Months: ITB therapy improved spasticity frequency and severity. Mean spasticity severity (AS) decreased from 3.78 at baseline to 1.48 at 12 months ($P = 0.00000014$). Mean spasm frequency (PSFS) decreased from 2.6 at baseline to 0.5 at 12 months ($P = 0.000017$).

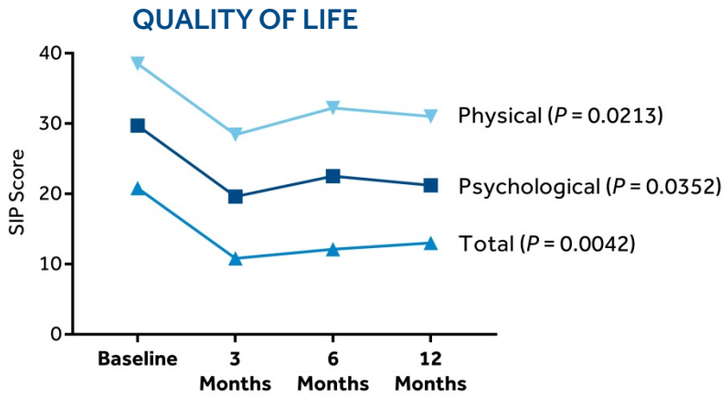
Dosing: Twelve month mean ITB dose was 298.44 mcg/day (range 23-775 mcg/day).

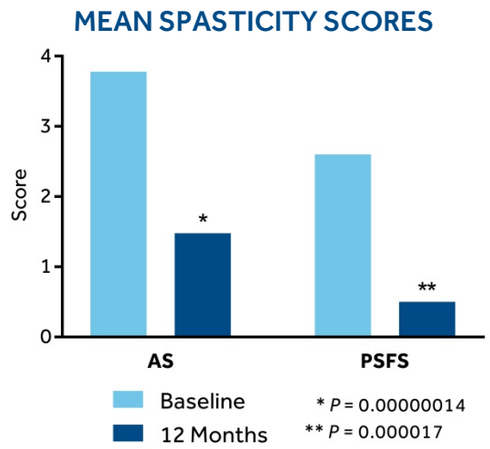
Adverse Events: One patient experienced a catheter complication requiring surgical revision.

KEY CONCLUSIONS

ITB therapy improved health-related quality life, spasticity severity, and spasm frequency at 12 month follow-up.

Limitations: The QLI tool was not developed for sensitivity to spasticity in MS and SCI patient populations, and may not have been a reliable choice for evaluating effects on quality of life with ITB therapy. In addition, a longer follow-up may have provided more data on the relationship between spasticity reduction and quality of life. The authors acknowledged that 12 months may not be long enough to see ITB therapy's impact on quality of life in domains such as psychological/spiritual and socioeconomic.





Acronyms: Ashworth Scale (AS); Ferrans and Powers Quality of Life Index (QLI); Multiple Sclerosis (MS); Penn Spasm Frequency Scale (PSFS); Sickness Impact Profile (SIP); Spinal Cord Injury (SCI).

INTRATHECAL BACLOFEN ADMINISTRATION FOR CONTROL OF SEVERE SPASTICITY: FUNCTIONAL IMPROVEMENT AND LONG-TERM FOLLOW-UP [117]

Azouvi P, Mane M, Thiebaut JB et al. *Arch Phys Med Rehabil.* 1996;77(1):35-39.

OBJECTIVE

This prospective open-label study assessed ITB therapy outcomes in 18 adult patients with severe spinal origin spasticity due to SCI (n=12), MS (n=4), or other cause (n=2). Mean patient age was 38.5 years (range 21-59 years). Patients were followed for mean 37.4 months (range 9-72 months), and 6 month outcomes were statistically analyzed. Outcome measures were spasticity severity (AS), spasm frequency (PSFS), disability (motor subset of FIM), dosing trends, and complications.

RESULTS

Spasticity Outcomes: Spasticity severity and frequency (AS and PSFS) improved by at least 2 points for all patients through follow-up. There was significant improvement in 6 month spasticity scores compared to baseline ($P < 0.001$ for both AS and PSFS).

Functional Outcomes: Mean motor FIM score improved from 39.9 at baseline to 58.5 at 6 months ($P < 0.001$). All FIM subscores, except for eating and stair climbing, were significantly improved. The nature and degree of improvement varied according to the type and level of spinal cord lesion:

- Patients with a thoracic or low cervical lesion (n=12) significantly improved in motor FIM score at 6 months ($P < 0.01$). The greatest improvement was observed in bathing, dressing lower body, and 3 items for transfers. Seven of 12 patients had improved locomotion, including better wheelchair positioning for 2 patients who, prior to ITB therapy, could not sit without being fastened. Five of 12 patients had improved walking ability, and 2 patients were able to climb stairs who could not prior to ITB therapy.
- Patients with severe impairment of upper limb motor function (n=6) had significant improvement in mean motor FIM score at 6 months ($P < 0.05$). There was little functional improvement in grooming, bathing, dressing, or transfers, as many patients had motor deficit or severe cerebellar syndrome and were dependent. Wheelchair sitting stability and comfort improved with ITB therapy, allowing for better locomotion. Transfer assistance and skin, bladder, and bowel care nursing tasks were easier.

Dosing: At implant, mean ITB dose was 142.8 mcg/day (range 20 to 425 mcg/day). Dose titration was necessary for 14 of 18 patients during the first 6 months to achieve optimal therapeutic benefit. The mean ITB dose was 312.1 mcg/day at 6 months, 339 mcg/day at 12 months, and stabilized thereafter. There was no significant difference in ITB dose according to the type, level, or severity of spinal cord lesion.

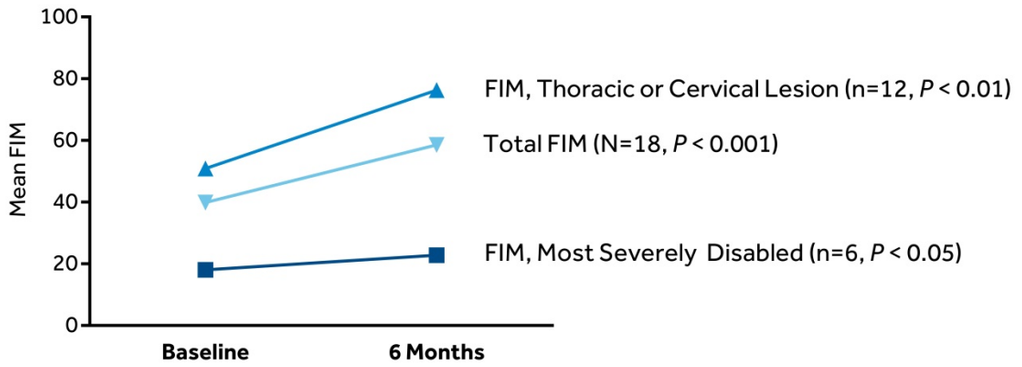
Adverse Events: Two patients experienced somnolence and muscle flaccidity, likely related to ITB overdose. One patient developed a subcutaneous infection at the pump pocket site shortly after implant, which resolved with local care. Four patients had catheter malfunction requiring surgical replacement (migration n=2, fracture n=1, kink n=1).

KEY CONCLUSIONS

ITB therapy is well received by patients. Functional benefit of ITB therapy is difficult to measure because there is high variability among patients. The use of a standardized scoring tool, such as the FIM, is valuable and can help in the assessment of ITB therapy benefit.

Limitations: The FIM does not provide a good measure of functional ability in patients who are totally dependent. Functional outcomes for the patients with severe impairment of upper limb motor function may have been more apparent on a different scale that was more focused on nursing tasks and transfers.

MEAN MOTOR FIM SCORES



Acronyms: Ashworth Scale (AS); Functional Independence Measure (FIM); Multiple Sclerosis (MS); Penn Spasm Frequency Scale (PSFS); Spinal Cord Injury (SCI).

CONTINUOUS INTRATHECAL BACLOFEN ADMINISTRATION BY A FULLY IMPLANTABLE ELECTRONIC PUMP FOR SEVERE SPASTICITY TREATMENT: OUR EXPERIENCE [121]

Guglielmino A, Sorbello M, Fazzio S et al. *Minerva Anestesiol.* 2006;72(10):807–820.

OBJECTIVE

In this prospective study, 30 adults with severe spasticity (mean age 51 years, range 36-67 years) were implanted with an intrathecal baclofen pump after a positive test dose. All 30 patients had a positive test dose of intrathecal baclofen (25 mcg to 100 mcg) and were implanted within 24 hours of the test dose. The origin of spasticity for the patients was MS (n=22), SCI (n=3), and other etiologies (n=5). The aim of the study was to evaluate, in patients with severe spasticity, the efficacy of ITB therapy after a follow-up period. Measured outcomes included complications and adverse events (intraoperative and postoperative), spasticity severity (AS), spasm frequency (PSFS), quality of life, quality of sleep, autonomy, and pain symptoms (VAS). The authors did not report the duration of follow up for outcomes measurements.

RESULTS

Spasticity Outcomes: The average spasticity severity and frequency (AS and PSFS) were significantly improved compared to baseline ($P < 0.0005$ for both).

Quality of Life Outcomes:

- Spasticity-related pain was significantly improved as measured by the 11-point VAS ($P < 0.005$)
- Quality of sleep improved as measured by the 5-point VAS ($P < 0.01$)
- Quality of life improved (personal hygiene, nutrition, ability to walk) as measured by the 5-point VAS ($P < 0.01$)
- Autonomy improved as measured by the 5-point VAS ($P < 0.01$)

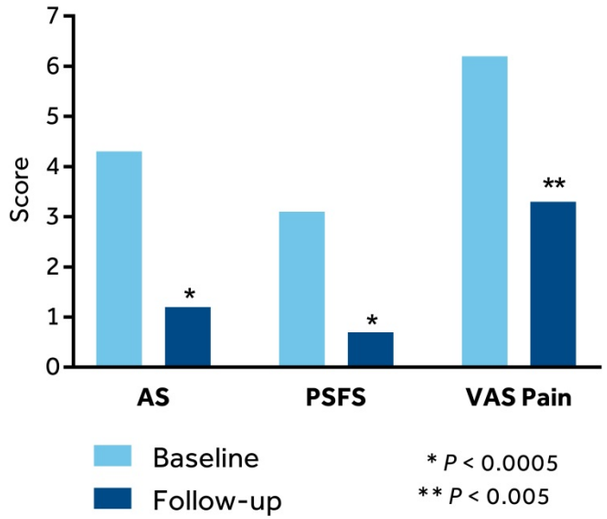
Adverse Events: Delayed surgical wound healing of the skin pocket was reported for 1 patient, who was diabetic. One patient experienced a catheter dislocation which was identified after sudden worsening in clinical response but without rebound effect. A pump malfunction (rotor malfunction) occurred in one patient 4 days postimplant. Rapid baclofen tolerance was observed in one patient 2 days post implant. Infusion with baclofen was discontinued and the patient was switched to morphine for 10 days. On day 11 ITB therapy was resumed and resulted in a good response.

KEY CONCLUSIONS

ITB therapy improved spasticity, pain, sleep quality, autonomy, and quality of life in adult patients with severe spasticity due primarily to MS and SCI.

Limitations: Sleep quality, autonomy, and quality of life were measured on a 5-point VAS adapted as a simplified version of the FIM and SIP. A VAS is well accepted for pain ratings but has limitations for assessing therapy outcomes such as quality of life.

MEAN SPASTICITY AND PAIN SCORES



Acronyms: Ashworth Scale (AS); Functional Independence Measures (FIM); Multiple Sclerosis (MS); Penn Spasm Frequency Score (PSFS); Sickness Impact Profile (SIP); Spinal Cord Injury (SCI); Visual Analog Scale (VAS).

CONTINUOUS INTRATHECAL BACLOFEN INFUSION BY A PROGRAMMABLE PUMP IN 131 CONSECUTIVE PATIENTS WITH SEVERE SPASTICITY OF SPINAL ORIGIN [124]

Ordia JI, Fischer E, Adamski E et al. *Neuromodulation*. 2002;5(1):16-24.

OBJECTIVE

A prospective study of ITB therapy for severe spasticity of spinal origin included 152 patients screened (151 with positive results) and 131 patients implanted with a pump (74 men and 57 women; mean age 42 years, range 17-73 years). A double-blind, randomized, placebo-controlled protocol was followed for the screening trial of the first 9 patients and the remaining 143 patients followed an open-label protocol without placebo for their screening. The origin of spasticity for the implanted patients was MS (n=63), SCI (n=53), and other etiologies (n=15). Duration of symptoms for the implanted patients averaged 14 years (range 5 months to 34 years). Mean follow up in the study was 73 months (range 2 to 137 months) and measured outcomes included spasticity severity (AS) and spasm frequency (PSFS).

RESULTS

Spasticity Outcomes: Mean spasticity severity and frequency (AS and PSFS) significantly improved compared to baseline ($P < 0.0005$ for both).

Functional Outcomes: While the authors did not specify measured functional outcomes, they noted the following:

- 18 ambulatory patients had improvements in gait and balance; two previously nonambulatory patients were able to walk.
- UDS in 8 patients demonstrated increased bladder capacity and reduced detrusor hyperreflexia and bladder-sphincter dyssynergy with ITB.

Dosing: Mean initial effective dose of ITB was 134 mcg/day (range 14 to 400 mcg/day). Nonambulatory patients required a significantly higher dose (mean 140 mcg/day) than ambulatory patients (mean 104 mcg/day, $P = 0.014$). The mean effective dose increased to 247 mcg/day by 6 months and to 277 mcg/day by 12 months. MS and SCI patients had similar effective doses initially and at 6 months; however, by 12 months SCI patient doses remained stable and MS patient doses continued to escalate.

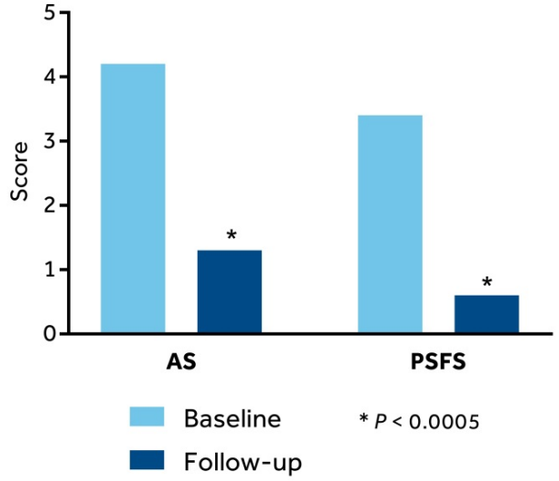
Adverse Events: Ten drug-related complications (spinal-type headache) were reported after the screening test. Postoperatively 34 drug-related complications were noted: constipation (n=12), muscular hypotonia (n=7), headache (n=6), urinary retention (n=4), hypotension and bradycardia (n=2), erectile dysfunction (n=2), and nausea/dizziness/drowsiness (n=1). Thirty-one device-related complications were reported including 24 catheter problems (12 occlusion/kinks, 8 breaks, 2 punctures, and 2 dislodgements). The remaining device-related complications included 2 flipped pumps, 2 pocket erosions, 1 stuck valve, 1 pocket infection and 1 case of bacterial meningitis. Ten patients died during follow-up though no deaths were attributed to ITB therapy.

KEY CONCLUSIONS

ITB therapy provided reduction in spasticity severity and spasm frequency. Increasing dosing profiles were observed; MS doses continued to increase through 12 months while SCI doses stabilized after 6 months. Following implant the most common drug-related complication was constipation, and the most common device-related complications were catheter problems including 12 occlusions or kinks.

Limitations: Functional outcomes were anecdotally reported by the authors.

MEAN SPASTICITY SCORES



Acronyms: Ashworth Scale (AS); Multiple Sclerosis (MS); Penn Spasm Frequency Score (PSFS); Spinal Cord Injury (SCI); Urodynamic Studies (UDS).

LONG TERM EFFECT (MORE THAN FIVE YEARS) OF INTRATHECAL BACLOFEN ON IMPAIRMENT, DISABILITY, AND QUALITY OF LIFE IN PATIENTS WITH SEVERE SPASTICITY OF SPINAL ORIGIN [127]

Zahavi A, Geertzen JH, Middel B et al. *J Neurol Neurosurg Psychiatry*. 2004;75(11):1553–1557.

OBJECTIVE

This observational follow-up study was a continuation to the double-blind and one year open-label results published by Middel et al. Long-term changes in impairment, disability, and functional status were assessed in 21 patients (12 men, 9 women; mean age 54.6 years, range 31-76 years) who received ITB therapy for mean 84.9 months (range 66-108). Spasticity was due to MS (n=11) and SCI (n=10). Outcomes were spasticity impairment (AS and PSFS, lower extremities only), disability (EDSS, AI, ISS), and health-related quality of life (SIP, HSCL). A non-standardized questionnaire was completed by patients to evaluate satisfaction.

RESULTS

Spasticity Outcomes: Compared to baseline, spasticity severity (AS) improved significantly at final assessment ($P = 0.00$) though it was not significantly different than at 26 weeks ($P = 0.95$). Spasm frequency (PSFS) also decreased significantly at final assessment compared to baseline ($P = 0.001$) and while the final measure was lower than at 26 weeks, the difference was not significant ($P = 0.26$). There were no significant differences between patients with MS and SCI.

Functional Outcomes: All disability measures worsened at the final assessment compared to baseline. There were no significant differences between patients with MS and SCI.

- Disability status (EDSS) significantly worsened at the final assessment compared to baseline ($P = 0.023$) and 26 weeks ($P = 0.031$).
- Ambulation (AI) significantly worsened at the final assessment compared to baseline ($P = 0.027$).
- Incapacity (ISS) significantly worsened at the final assessment compared to baseline ($P = 0.011$) and 26 weeks ($P = 0.016$).

Health-Related Quality of Life Outcomes: There were no significant changes in SIP or HSCL at final assessment compared to baseline. A single SIP category, psychosocial dimension, significantly worsened at the final assessment ($P = 0.01$).

Patient Satisfaction: Most patients (19 of 21) were satisfied with the overall treatment.

Dosing: The mean dose at the final evaluation was 290.63 mcg/day. The mean of the maximum patient doses over the entire treatment period was 481.91 mcg/day. There was no statistically significant difference in dosing between patients with MS and SCI.

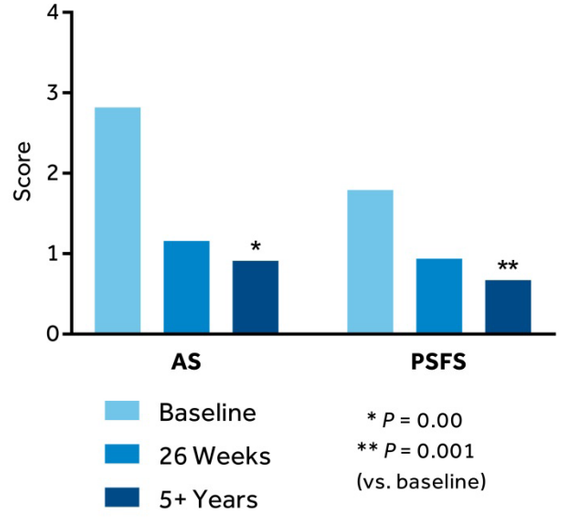
Adverse Events: Of complications reported more than once, there were 70 drug-related, 27 catheter-related, 14 surgery-related, 4 pump-related, and 2 other technical/surgical complications. Drug-related events were muscle weakness (n=16), somnolence/tiredness (n=13), respiratory difficulty (n=6), dysarthria (n=6), psychiatric (n=5), dizziness (n=4), hypotension (n=3), epileptic insults (n=3), and other (n=14). Two patients each experienced 5 catheter dysfunctions. System explant was required due to meningitis in one patient and persistent fever from bacteremia in another patient. These patients were likely reimplanted (termed "temporary removals").

KEY CONCLUSIONS

Patients receiving ITB therapy for at least 5 years significantly improved in spasticity impairment. A small but statistically significant worsening in disability status and psychosocial aspects of perceived health status was observed in long-term follow-up. Most patients expressed satisfaction with the therapy.

Limitations: An attrition rate of 45% (21 of 38 patients in the original study) may bias the results toward patients who had better general outcomes. The long-term follow-up measurements and assessments were performed by a different observer than those involved in the initial study and interobserver variability may exist.

MEAN SPASTICITY SCORES



Acronyms: Ambulation Index (AI); Ashworth Scale (AS); Expanded Disability Status Scale (EDSS); Hopkins Symptom Checklist (HSCL); Incapacity Status Scale (ISS); Multiple Sclerosis (MS); Penn Spasm Frequency Scale (PSFS); Sickness Impact Profile (SIP); Spinal Cord Injury (SCI).

EFFECT OF INTRATHECAL BACLOFEN DELIVERED BY AN IMPLANTED PROGRAMMABLE PUMP ON HEALTH RELATED QUALITY OF LIFE IN PATIENTS WITH SEVERE SPASTICITY [1,2,3]

Middel B, Kuipers-Upmeijer H, Bouma J et al. *J Neurol Neurosurg Psychiatry*. 1997;63(2):204–209.

OBJECTIVE

A prospective, double-blind, randomized study compared ITB therapy to placebo in 22 patients (10 men, 12 women; mean age 48.3 years, range 19-70 years) with MS (n=13) and SCI (n=9). Twelve patients received ITB and 10 received intrathecal placebo for 3 months in a double-blind phase. The patients receiving placebo were implanted for ITB therapy, and all were then followed to 12 months in an observational phase. Spasticity severity (AS), spasm frequency (PSFS), self-reported pain, and health-related quality of life (SIP and HSCL) measures were collected. Outcome measures from baseline to 3 months were compared within the baclofen and placebo groups as well as between groups. Outcome measures at 12 months with ITB therapy were compared to baseline. Complications were not reported.

RESULTS

Health-Related Quality of Life Outcomes:

ITB vs. placebo at 3 months: There were no significant differences in the ITB cohort's SIP or HSCL scores compared to placebo.

ITB therapy, 12 months vs. baseline: There were statistically significant improvements in all SIP categories (all $P \leq 0.04$) except the Psychosocial dimension, and two of three HSCL categories (both $P = 0.01$) in ITB patients.

Spasticity and Spasticity-Related Pain Outcomes:

ITB vs. placebo at 3 months: ITB patients had a significantly greater improvement in PSFS ($P < 0.05$), AS ($P < 0.01$), and self-reported pain scores ($P < 0.05$) compared to placebo.

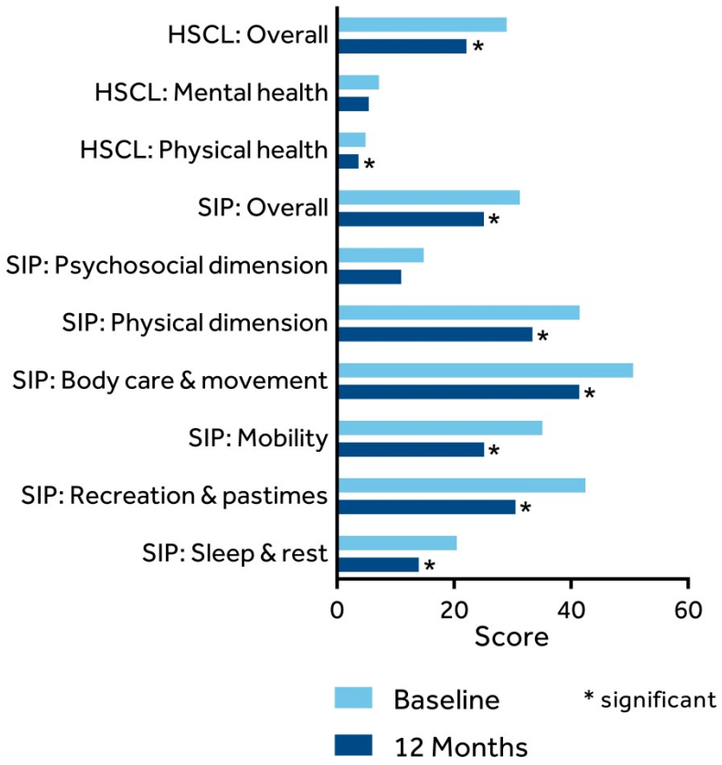
ITB therapy, 12 months vs. baseline: All ITB patients had significantly improved spasticity and pain scores. PSFS improved from mean 2.16 to 0.62 ($P = 0.003$), AS improved from mean 2.87 to 0.44 ($P = 0.002$), and pain score improved from mean 4.57 to 1.97 ($P = 0.009$).

KEY CONCLUSIONS

Clinical efficacy (PSFS, AS, pain) was significantly better for patients receiving ITB therapy compared to placebo at 3 months, and compared to baseline at 12 months. Significant improvements were observed at 12 months compared to baseline for most measures of health-related quality of life.

Limitations: Due to the double-blind design of the randomized phase of the study, the protocol limited physicians to 2 changes in infusion rate or drug concentration. Therefore, optimal ITB therapy dosing may not have been achieved in the first 3 months of the study.

MEAN QUALITY OF LIFE SCORES



Acronyms: Ashworth Scale (AS); Hopkins Symptom Checklist (HSCL); Penn Spasm Frequency Scale (PSFS); Sickness Impact Profile (SIP).

FUNCTIONAL IMPROVEMENT IN PATIENTS WITH SEVERE SPINAL SPASTICITY TREATED WITH CHRONIC INTRATHECAL BACLOFEN INFUSION [118]

Dario A, Scamoni C, Bono G et al. *Funct Neurol.* 2001;16(4):311–315.

OBJECTIVE

A retrospective analysis of efficacy and functional benefits was conducted in 20 non-ambulatory patients (9 men, 11 women; mean age 39.1 years, range 27-52 years) with severe spasticity due to MS (n=13), SCI (n=4), or other causes (n=3). Minimum follow-up time was 12 months, and mean follow-up was 22.4 months. Outcome measures were spasticity severity (AS), spasm frequency (SFS), self-reported pain, and physical disability (FIM).

RESULTS

Spasticity and Pain Outcomes: Spasticity severity (AS) and spasm frequency (SFS) improved significantly at final assessment as compared to baseline ($P < 0.01$). Self-reported pain scores also improved significantly ($P < 0.05$).

Functional Outcomes: Mean FIM score improved from 33.8 at baseline to 58.7 at final assessment ($P < 0.05$).

- Most significant improvement was noted for bathing, dressing the lower body, and transferring the body.
- There was minimal improvement in 2 patients with tetraparesis (all other patients had paraparesis).
- Two patients resumed work.
- There was no significant difference in FIM results between MS and SCI patients.

Dosing: Mean ITB dose was 295 mcg/day (range 90 – 830 mcg/day). Progressive dose increase was needed in 5 patients after pump implant.

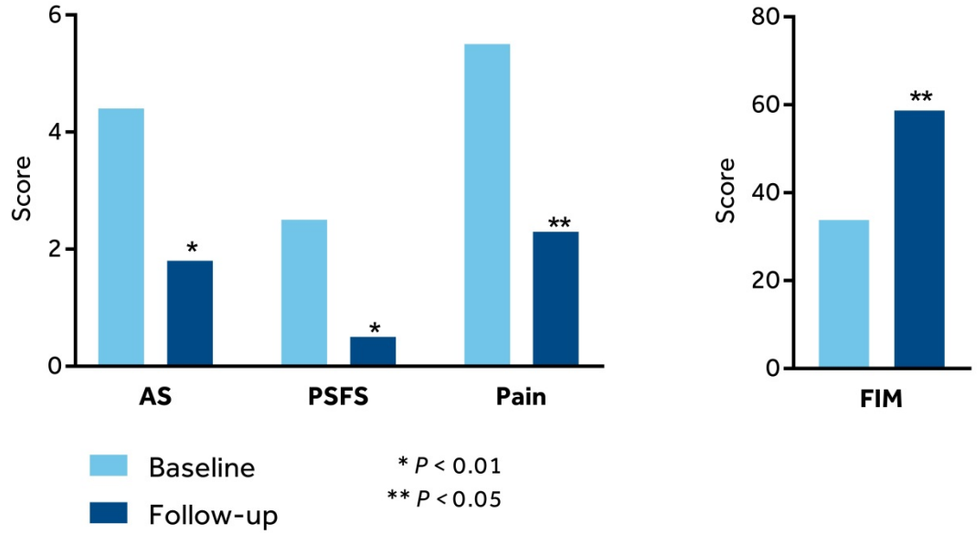
Adverse Events: One patient experienced a CSF leak around the catheter that required surgical repair.

KEY CONCLUSIONS

Functional improvements were observed with ITB therapy, most markedly in bathing, dressing the lower body, and transferring the body. Spasticity severity, spasm frequency, and self-reported pain also significantly improved with ITB therapy.

Limitations: The SFS score was based on a subset of 13 patients. The rationale for SFS data based on a subset was not specified.

MEAN SPASTICITY, PAIN, AND FUNCTIONAL SCORES



Acronyms: Ashworth Scale (AS); Cerebrospinal fluid (CSF); Functional Independence Measure (FIM); Multiple Sclerosis (MS); Spasm Frequency Scale (SFS); Spinal Cord Injury (SCI).

INTRATHECAL BACLOFEN IN MULTIPLE SCLEROSIS AND SPINAL CORD INJURY: COMPLICATIONS AND LONG-TERM DOSAGE EVOLUTION [119]

Draulans N, Vermeersch K, Degraeuwe B et al. *Clin Rehabil*. 2013;27(12):1137-1143.

OBJECTIVE

A long-term retrospective analysis was performed in order to evaluate dosing changes and complications in 130 patients with severe spasticity due to MS (n=81) or SCI (n=49). The mean follow-up was 63 months, comprising 797 pump years. The MS patients included 32 men and 49 women with a mean age of 49 years and mean follow-up of 63 months. The SCI patients included 41 men and 8 women with a mean age of 38 years and mean follow-up of 92 months. Complications were defined as those requiring surgical reintervention, those involving a CSF leak, and pharmacologic adverse events requiring treatment besides pump refill or dosage change.

RESULTS

Dosing: The mean ITB dose at 3 months was 216 mcg/day. There was no significant difference between the MS and SCI patient groups in ITB dosing for the first 2 years.

- For MS patients the daily dose appeared to stabilize after 2 years (mean 323 mcg/day)
- For SCI patients the daily dose stabilized around 5 years at a higher daily dose (mean 504 mcg/day).

Adverse Events: A total of 104 complications were observed, corresponding to a rate of 0.011 complications per month. There was no difference in complication rates between the MS and SCI patient groups. Complication rates during the first year ($P = 0.003$) and the sixth year ($P = 0.012$) were significantly higher. Most complications were related to the catheter (n=78). Two serious pharmacologic adverse events occurred; both involved overdosing in an MS patient with resulting respiratory problems requiring observation in an ICU. Two complications led to discontinuation of ITB therapy: gut perforation during pump placement and pump infection. In 3 other cases of pump infection, the pump was explanted and then reimplanted after antibiotic treatment.

KEY CONCLUSIONS

The estimated complication rate for ITB therapy was 1% per month, with most complications being catheter-related. ITB dosage stabilized in the long term, suggesting that long-term tolerance to ITB is not present.

Type of Complication		No. MS Patients	No. SCI Patients
Surgical		7	9*
Infection	Meningitis	0	0
	Pump infection	0	4
Gut perforation		1	0
Hematoma around pump (surgery needed)		1	0
CSF leak	Need for surgery/blood patch	2	2
	Headache, no intervention	2	0
Wound dehiscence		1	2
Drug delivery system		43	43
Catheter-related	Obstruction	3	6
	Migration	4	3
	Kink	4	2
	Disconnection	2	5
	Fracture	3	3
	Tear	7	2
	Unknown	17	17
Pump-related	Dysfunction	2	3
	Pump tilting	1	0
	Volume discrepancy	0	2
Serious pharmacological adverse events		2	0
Overdose causing respiratory distress		2	0

** Potential typographical error: Paper reported 9 surgical complications but the corresponding numbers add up to 8.*

Acronyms: Cerebrospinal Fluid (CSF); Intensive Care Unit (ICU); Multiple Sclerosis (MS); Spinal Cord Injury (SCI).

INTRATHECAL BACLOFEN THERAPY AND MULTIPLE SCLEROSIS: OUTCOMES AND PATIENT SATISFACTION [125]

Vender JR, Hughes M, Hughes BD et al. *Neurosurg Focus*. 2006;21(2):e6.

OBJECTIVE

This retrospective study included 20 ITB patients (16 women, 4 men; mean age 51 years) who completed a survey about their overall satisfaction with ITB therapy. Mean time after pump implant was 31.9 months. The survey was a multipoint data collection tool designed to assess status in 4 dimensions: activities of daily living (ADLs), musculoskeletal, mobility, and functional improvement.

RESULTS

Oral Medication Use:

- Prior to ITB, 18 of 20 patients were treated with oral baclofen; with ITB 14 patients discontinued and 4 reduced their dose.
- Prior to ITB, 6 of 20 patients were treated with muscle relaxants (Zanaflex or Flexeril); after ITB 3 patients discontinued and 3 reduced their dose.

Status Assessment:

- ADLs: There were no significant changes with ITB therapy.
- Musculoskeletal: The estimated spasm frequency per day reduced from a mean of 44.5% to 21%. Comfort level improved after surgery. Ability to stand did not change meaningfully after surgery, and worsened at last follow-up.
- Mobility: There were no alterations in mobility with ITB therapy. Fine motor coordination worsened at last follow-up visit.
- Functional: Cognition and ability to sleep did not significantly change with ITB therapy. Energy level increased somewhat immediately after implant, but was similar to preimplant levels at last follow-up. Self-esteem/body image worsened somewhat after pump placement.

Caregiver Assessment: Ten caregivers were asked about their ability to care for the patients after pump implant, with 7 stating that it had improved, 2 that it had not changed, and 1 that it had worsened.

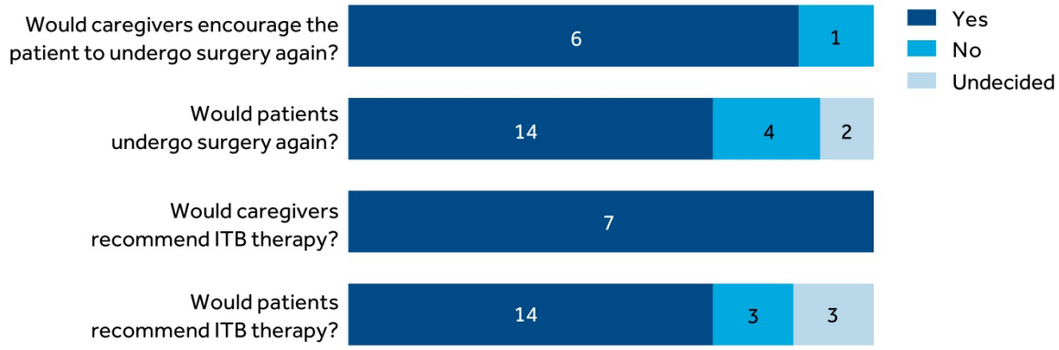
Adverse Events: There were no complications related to the implant procedure and no system-related revisions were required during follow-up.

KEY CONCLUSIONS

Most patients and caregivers in this study were satisfied with the pump and reported a reduction in spasm frequency after implant. Most caregivers also reported improvements in their ability to care for their patients after initiation of ITB therapy.

Limitations: Patients and caregivers were asked to rate outcomes presently and in the past. This may introduce recall bias. Additionally, the authors did not specify whether the survey was a validated tool to measure outcomes, and the results were reported without providing indication of statistical significance.

PATIENT AND CAREGIVER SATISFACTION



Acronyms: Activities of Daily Living (ADLs); Multiple Sclerosis (MS).

CLINICAL OUTCOME AND COMPLICATIONS OF INTRATHECAL BACLOFEN PUMP IN MULTIPLE SCLEROSIS PATIENTS: A RETROSPECTIVE STUDY [122]

Khan AA, Birks-Agnew I, Bullock P, Rushton D. *NeuroRehabilitation*. 2010;27(2):117-120.

OBJECTIVE

A retrospective cohort study presented outcomes of 40 patients with severe, advanced MS who received ITB therapy between 1996 and 2007. Patient age ranged from 16 to 46 years at diagnosis and 28 to 61 years at pump implant. Mean follow-up was 5.25 years (range 5 months -12.5 years), with 81% of patients followed for at least 2 years. Information from patient files was evaluated including spasticity severity (MAS), spasm frequency in the lower limbs (PSFS), and complications.

RESULTS

Spasticity Outcomes: Spasticity severity (MAS) was reduced from a mean of 4.6 (range 3 – 5) prior to implant to a mean of 1.0 (range 0 – 4) at the most recent follow-up. Similarly, spasm frequency (PSFS) was also reduced from a mean of 3.6 (range 1 – 4) prior to implant to a mean of 1.1 (range 0 – 2) at the most recent follow-up. Measures of statistical significance were not noted.

Dosing: At 1 year postimplant, the mean dose was 209 mcg/day (range 24 to 449 mcg/day). At the most recent follow-up the mean was 285 mcg/day (range 0 to 1300 mcg/day).

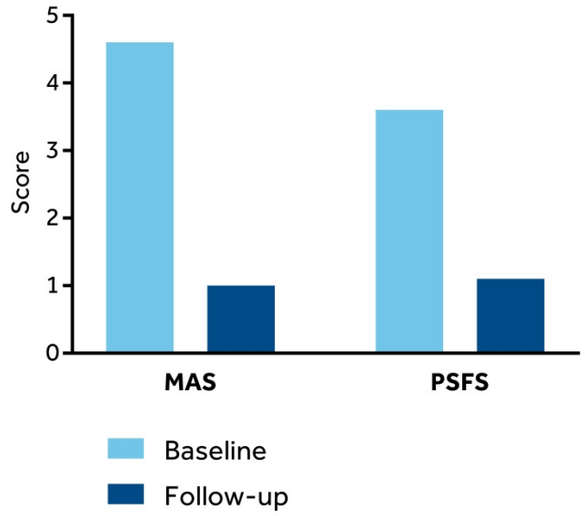
Adverse Events: No adverse effects were noted from the screening test dose. Six patients had postimplant complications; most were catheter-related. Complications included catheter migration (n=2), discontinuity in the catheter (n=1), fault in the delivery system (n=1), seroma (n=1), and deep vein thrombosis and pulmonary embolism (n=1). Seven pumps were replaced electively, mostly due to end of battery life but also due to pump flipping. Two patients requested to have their pumps removed due to drug side effects, though neither elected to have it removed when their ITB dose was reduced and spasticity increased.

KEY CONCLUSIONS

ITB therapy reduced spasticity severity and spasm frequency.

Limitations: While reductions in MAS and PSFS were noted, measures of statistical significance were not included.

MEAN SPASTICITY SCORES



Acronyms: Modified Ashworth Scale (MAS); Multiple Sclerosis (MS); Penn Spasm Frequency Scale (PSFS).

CLINICAL AND SAFETY EVIDENCE: **MIXED POPULATION STUDIES**

Lead Author	Year	Abbreviated Title	Journal	Page
Gooch JL	*2004*	Care provider assessment of ITB in children	*Dev Med Child Neurol*	64
Stempien L	*2000*	ITB pump use for spasticity: A clinical survey	*Am J Phys Med Rehabil*	65
Creedon SD	*1997*	ITB for severe spasticity: A meta-analysis	*Int J Rehabil Health*	66
Staal C	*2003*	A self-report of quality of life of patients receiving ITB therapy	*Rehabil Nurs*	67
Ucar T	*2011*	Outcomes of ITB therapy in spasticity	*Turk Neurosurg*	68
Mathur SN	*2014*	Long-term ITB: Outcomes after more than 10 years of treatment	*PM R*	69
Saval A	*2010*	ITB for spasticity management: A comparative analysis of spasticity of spinal vs cortical origin	*J Spinal Cord Med*	70
Guillaume D	*2005*	A clinical study of intrathecal baclofen using a programmable pump for intractable spasticity	*Arch Phys Med Rehabil*	71
Natale M	*2012*	Intrathecal baclofen therapy for severe spasticity: analysis on a series of 112 consecutive patients and future prospectives	*Clin Neurol Neurosurg*	72
Delhaas EM	*2008*	Long-term outcomes of continuous intrathecal baclofen infusion for treatment of spasticity: a prospective multicenter follow-up study	*Neuromodulation*	73
Taira T	*2013*	Rate of complications among the recipients of intrathecal baclofen pump in Japan: A multicenter study	*Neuromodulation*	74
Dvorak EM	*2010*	Incidence and identification of intrathecal baclofen catheter malfunction	*PM R*	75
Borrini L	*2014*	Occurrence of adverse events in long-term intrathecal baclofen infusion: A 1-year follow-up study of 158 adults	*Arch Phys Med Rehabil*	76
Gooch JL	*2003*	Complications of intrathecal baclofen pumps in children	*Pediatr Neurosurg*	77
Motta F	*2014*	Analysis of complications in 430 consecutive pediatric patients treated with ITB therapy: 14-year experience	*J Neurosurg Pediatr*	78
Vender JR	*2006*	Identification and management of ITB pump complications: a comparison of pediatric and adult patients	*J Neurosurg Pediatr*	79
Dickey MP	*2013*	Infectious complications of ITB pump devices in a pediatric population	*Pediatr Infect Dis J*	80
Haranhalli N	*2011*	ITB therapy: complication avoidance and management	*Childs Nerv Sys*	81

CARE PROVIDER ASSESSMENT OF INTRATHECAL BACLOFEN IN CHILDREN [134]

Gooch JL, Oberg WA, Grams B, Ward LA, Walker ML. *Dev Med Child Neurol.* 2004;46(8):548–552.

OBJECTIVE

In a study designed to gather perceptions about ITB therapy, caregivers for 80 children and young adults (mean age 11 years, range 3*-21 years) were interviewed at least 1 year after initiation of ITB therapy. All patients were treated with ITB for severe spasticity due to CP (n=62), BI (n=10), SCI (n=1), or other causes (n=7). The majority of patients had spastic quadriplegic CP (n=55) and were GMFCS levels IV or V. Patients were evaluated for range of motion, spasticity severity (AS), goal achievement (5-point scale), and quality of life (Personal Care, Positioning, and Comfort sections of the Rehabilitation Institute of Chicago Caregiver Questionnaire).

RESULTS

Range of Motion and Spasticity:

- Most patients experienced a rapid and lasting reduction in spasticity as measured by the Ashworth Scale. The majority of patients had a reduction of 0-0.9 in the upper extremities and 1-1.9 in the lower extremities.
- Of 51 patients with lower extremity range of motion measurements, range of motion was maintained in 43 (84%), and reduced in 8 (16%).

Goal achievement and quality of life: The most common treatment goals were decreased pain/improved comfort, prevented worsening of deformities, and improved ease of care. These goals were achieved by 91%, 91%, and 88% of patients, respectively.

Adverse Events: Sixty-three patients experienced 70 device-related events requiring surgery; the most common were catheter occlusion/angulation (n=12 events), dislodgment from the intrathecal space (n=12), and disconnection at the pump (n=11). Device-related complications not requiring surgery were CSF leak (n=4), flipped pump (n=2), and suture site inflammation (n=2). Non-device-related complications were cognitive status change (n=2), severe spasms (n=1), and overdose (n=1).

KEY CONCLUSIONS

Children and young adults with severe intractable spasticity, particularly those who have difficulty standing and ambulating, may show more improvement with ITB therapy through goals focused on comfort and care rather than functionality such as assisting with transfers and assisted walking.

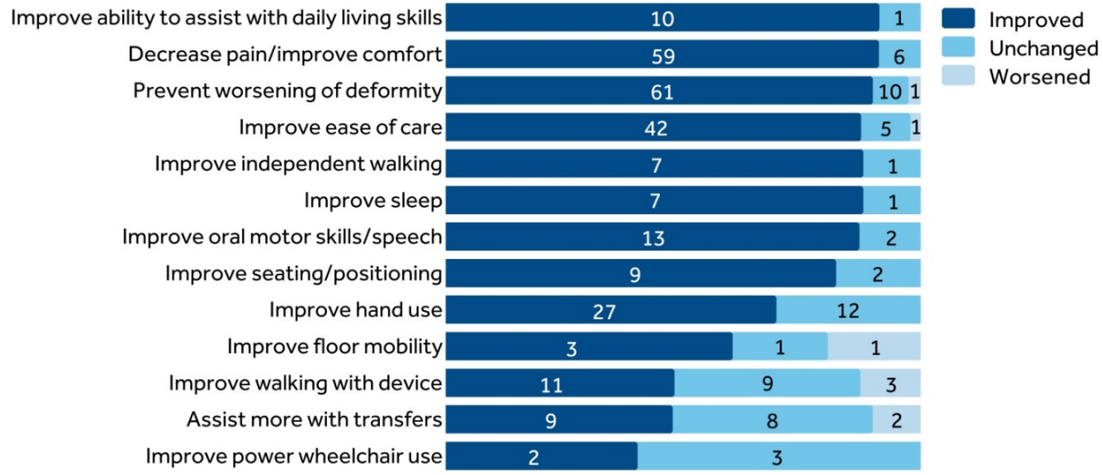
Limitations: The study was observational and not powered for statistical analysis, but the primary goal was to collect caregivers' perceptions of ITB therapy which is a qualitative measurement.

CHANGE IN ASHWORTH SCORE

(by count of patients)

GOAL ACHIEVEMENT WITH ITB THERAPY

(by count of patients)



** Safety and effectiveness of ITB therapy in patients under the age of 4 has not been established.*

Acronyms: Ashworth Scale (AS); Brain Injury (BI); Cerebral Palsy (CP); Cerebrospinal Fluid (CSF); Spinal Cord Injury (SCI).

INTRATHECAL BACLOFEN PUMP USE FOR SPASTICITY: A CLINICAL SURVEY [142]

Stempien L, Tsai T. *Am J Phys Med Rehabil.* 2000;79(6):536-541.

OBJECTIVE

Forty U.S. centers were surveyed on clinical practices and experiences with ITB therapy. Completed responses were received for 936 patients treated with ITB therapy for severe spasticity due to CP (n=412), SCI (n=206), BI (n=84), or other causes (n=234). Of the 40 facilities surveyed, 17 were children's hospitals, 15 were general hospitals, 7 were rehabilitation hospitals, and 1 was an outpatient facility.

RESULTS

Complications during implant hospitalization: Mechanical and medical complications may occur during implant hospitalization. Common medical complications included constipation (2.9%) and infection (1.6%). Common surgical complications included CSF leak (2.2%) and CSF collection (3.3%). One center had 9 patients with CSF collection. After reviewing these data, the surgeon changed surgical technique and no additional CSF collections occurred.

Long-term complications: Complications reported after the initial implant hospitalization were low. The most common complication was infection in 16 (1.7%) patients. Seroma or CSF collection was reported in 8 patients (0.8%).

Device-related complications: At the time of the survey, 66 pumps and 64 catheters had been replaced. The most common reason for pump replacement was infection (n=16, 1.7%) or end-of-battery life (n=12, 1%). The most common reason for catheter replacement was catheter kinking or migration (n=40, 4%).

KEY CONCLUSIONS

Reported complications following ITB pump implant and in the long-term were low, and the risk of CSF leak and CSF collection was successfully mitigated by changing surgical technique.

Acute complications during implant hospitalization	%
CSF collection	3.3%
Constipation	2.9%
Headache	2.4%
CSF leak	2.2%
Infection	1.6%
Hypotension	0.9%
Hematoma	0.8%
Hydrocephalus	1 case
Worsened gait	1 case
Urine retention	1 case
Flipped pump	1 case
Catheter revision	2 cases
Total	**15%**

Reason for pump replacement	No. of Patients	%
Infection	16	1.7%
Battery failure	12	1%
Patient request	11	1%
Hypermobility with effusion	8	<1%
Pump failure	4	<1%
CSF leak	2	<1%
Dehiscence	1	<1%
Smaller pump placed	1	<1%
Cause unknown	11	1%
Total	**66**	**7%**
Not incl. battery replacement	**47**	**5%**

Reason for catheter replacement	No. of Patients	%
Kinks/migration	40	4%
Infection	3	<1%
Occlusion	1	<1%
Arachnoiditis	1	<1%
Cause not stated	19	2%
Total	**64**	**7%**

Acronyms: Brain Injury (BI); Cerebral Palsy (CP); Cerebrospinal Fluid (CSF); Spinal Cord Injury (SCI).

INTRATHECAL BACLOFEN FOR SEVERE SPASTICITY: A META-ANALYSIS [129]

Creedon SD, Dijkers MP, Hinderer SR. *Int J Rehabil Health*. 1997;3(3):171–185.

OBJECTIVE

A retrospective, meta-analysis was conducted on English language studies (published prior to June 1996) concerning ITB therapy for severe spasticity. Twenty-seven studies comprising 490 patients were deemed appropriate for inclusion in the meta-analysis. SCI was the most frequent etiology (42% of patients), followed by MS (33%), CP (12%), and other causes (13%). The average patient age was 36 years old, was 7 years post the onset of their CNS disorder, and had 18 months of ITB therapy follow-up data. Complications were not reported.

RESULTS

Spasticity Outcomes: Calculated across studies (weighted by sample size), mean AS scores decreased from 3.9 to 1.6 and mean PSFS scores decreased from 3.5 to 0.7 (correlated t-test $P < 0.001$ for AS and PSFS scores). Effect sizes, as calculated by Glass' Δ, were positive for all studies, ranging from 1.12 to 13.0. Differences in AS and PSFS scores were significantly lower with ITB in each diagnostic group ($P < 0.001$ for all groups and measures).

Success Rate: The overall success rate for ITB therapy was 78.1%. To estimate this rate, the proportions successful at each stage (screening test, implant, and 1 year post implant) were multiplied.

Dosing: Dosages were statistically significantly different between diagnostic groups ($P = 0.001$). The authors estimated dosage creep to be approximately 15% per month. At an average of 1.8 years postimplant the dose for each group was:

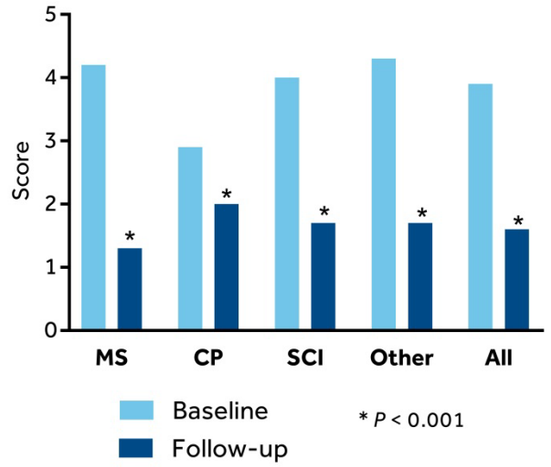
- 205 ± 136 mcg/day in 49 MS cases
- 372 ± 315 mcg/day in 68 SCI cases
- 246 ± 192 mcg/day in 23 other diagnoses
- There were only 2 cases of current dosage data for CP, therefore CP dosages were not averaged.

KEY CONCLUSIONS

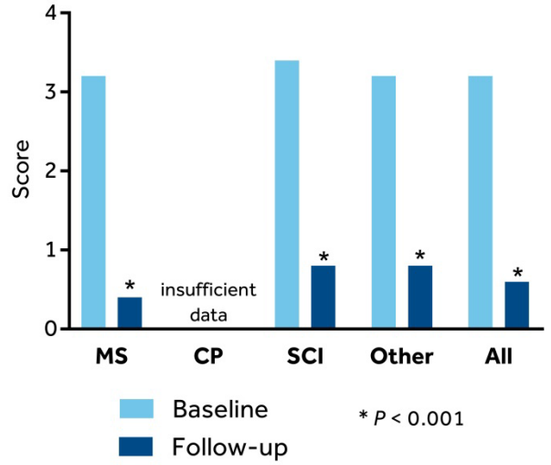
ITB therapy significantly improves spasticity. Doses vary between diagnostic groups.

Limitations: Conclusions regarding ITB effectiveness are limited due to the fact that results were primarily based on pre- and post-ITB AS and PSFS scores. In most cases examiners were not blinded and most studies did not include a control group or crossover design.

CHANGE IN ASHWORTH SCORE



CHANGE IN PSFS SCORE



Acronyms: Ashworth Scale (AS); Central Nervous System (CNS); Cerebral Palsy (CP); Multiple Sclerosis (MS); Penn Spasm Frequency Scale (PSFS); Spinal Cord Injury (SCI).

A SELF-REPORT OF QUALITY OF LIFE OF PATIENTS RECEIVING INTRATHECAL BACLOFEN THERAPY [141]

Staal C, Arends A, Ho S. *Rehabil Nurs*. 2003;28(5):159-163.

OBJECTIVE

A single-center, retrospective, questionnaire-based study evaluated ITB therapy's effect on quality of life (QoL) in 49 patients (30 adult, 19 pediatric) with severe spasticity due to CP (n=22), SCI (n=14), BI (n=11), and MS (n=4). One patient had both CP and SCI and 2 patients had both BI and SCI. Follow-up times ranged from less than 6 months to over 5 years, with 73% of patients having at least 1 year of follow-up.

RESULTS

Quality of Life Outcomes: QoL was measured based on a survey of whether the patient believed that ITB therapy improved his or her quality of life. Forty-three patients (88%) responded that their QoL had improved, 4 (8%) responded that they were not sure, and 2 (4%) said that their QoL had not improved. Patients were also asked to indicate the areas of greatest impact on QoL and were not limited in the number of areas they could select. The most frequently marked areas were spasticity control without sedative effect (n=35, 71.4%) and ease of care for caregivers (n=30, 61.2%). Forty-six (93.8%) patients responded that they would recommend ITB to others. The remaining 3 did not answer the question.

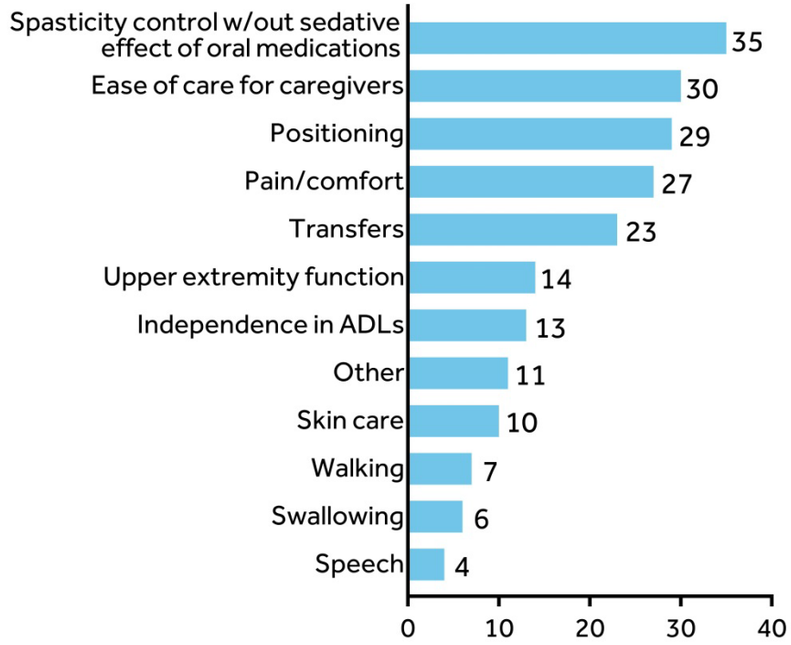
Adverse Events: Adverse events were self-reported by patients or their caregivers in the questionnaire. Nineteen (38.8%) patients reported complications with their pumps. Complications included infection (n=5), catheter disconnect/breakage (n=5), premature battery failure (n=2), and other (n=11). Comments provided for "other" complications included increased spasticity when pump was low or empty; flipped pump; blood patch, headaches and vomiting and weight loss; withdrawal before alarm date; convulsions after refill; and report of pump hitting the patients ribs when standing and rolling.

KEY CONCLUSIONS

A majority of patients responded to the questionnaire that they believed that their QoL had improved. Most patients responded that they would recommend baclofen to others. The areas of greatest impact on QoL were spasticity control without sedative effect and ease of care for caregivers.

Limitations: A standardized QoL tool was not utilized. Adverse events were based on patients self-reporting and not based on an examination of the patients' medical records. The spasticity etiology numbers provided by the authors did not add up to the total 49-patient population.

ITB THERAPY: AREAS OF GREATEST IMPACT ON QUALITY OF LIFE



Acronyms: Brain Injury (BI); Cerebral Palsy (CP); Multiple Sclerosis (MS); Quality of Life (QoL); Spinal Cord Injury (SCI).

OUTCOMES OF INTRATHECAL BACLOFEN (ITB) THERAPY IN SPASTICITY [144]

Ucar T, Kazan S, Turgut U, Samanci, NK. *Turk Neurosurg.* 2011;21(1):59-65.

OBJECTIVE

A single-center retrospective chart review evaluated outcomes of 30 patients (19 male, 11 female; mean age 30.1 years, range 5-67 years) who were implanted for ITB therapy. Severe spasticity was caused by CP or BI (n=18) and SCI (n=12). Mean (± SD) follow-up was 27.60 ± 14.66 months (range 1-62 months). Outcome measures were spasticity severity (AS) in upper and lower extremities, spasm frequency (SFS) in upper and lower extremities, activities of daily living (BI), pain (VAS), and handicap (RS).

RESULTS

Spasticity Outcomes: Spasticity severity (AS) and spasm frequency (SFS) significantly improved in all patients. Scores decreased within the first year and then generally stabilized. Means scores were statistically significantly lower with ITB therapy than before in both the upper and lower extremities. Pain scores were also significantly lower with ITB therapy.

Functional Outcomes: Mean score for activities of daily living improved significantly ($P < 0.005$). Improvements in motor function were most significant within the first year. In all patients, facilitation of transfer, active and passive physical therapy, and nursing care was observed. A significant reduction in handicap (RS) was also observed ($P < 0.005$).

Dosing: The mean initial ITB dose was 140 mcg/day (range 90 to 340 mcg). Dosages progressively increased during the first year in all patients, then stabilized for all but 4 patients in whom further dose adjustment was required.

Twelve months after implant, dosages were:

- 90 – 120 mcg/day (n=9)
- 120 – 170 mcg/day (n=14)
- 170 – 240 mcg/day (n=3)
- 240 – 270 mcg/day (n=3)
- 340 mcg/day (n=1)

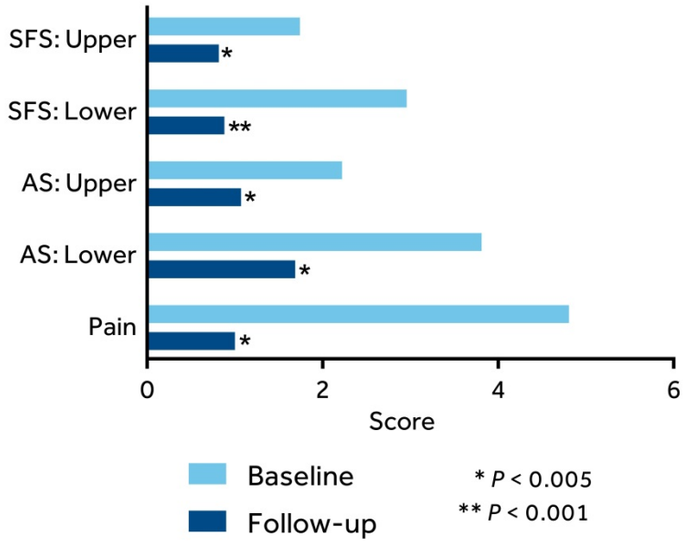
Adverse Events: During the screening test the most common complications were nausea/vomiting (1.6%) and sedation (2.4%). One infection occurred, requiring pump explant and reimplant 3 months later. The most frequent surgical complication was CSF collection, seen primarily in pediatric patients. The most common technical complication was a broken or retracted catheter (16.6%). The authors did not report if there were other surgical or technical complications.

KEY CONCLUSIONS

Spasticity severity, spasm frequency, and pain were significantly reduced with ITB therapy in patients with spasticity of both cerebral and spinal origin. Functional outcomes of activities of daily living and handicap were also significantly improved with ITB therapy.

Limitations: This retrospective study did not include a control group for comparison. Detailed results by patient showed some missing follow-up data and inconsistencies in spasticity etiology, which was not addressed by the authors.

MEAN SPASTICITY SCORES



Acronyms: Ashworth Scale (AS); Barthel Index (BI); Brain Injury (BI); Cerebral Palsy (CP); Cerebrospinal Fluid (CSF); Rankin Scale (RS); Spasm Frequency Scale (SFS); Spinal Cord Injury (SCI); Standard Deviations (SD); Visual Analog Scale (VAS).

LONG-TERM INTRATHECAL BACLOFEN: OUTCOMES AFTER MORE THAN 10 YEARS OF TREATMENT [137]

Mathur SN, Chu SK, McCormick Z et al. *PM R*. 2014;6(6):506-513.

OBJECTIVE

This cross-sectional survey and retrospective chart review evaluated long-term outcomes with ITB therapy for 24 patients with severe spasticity (11 male, 13 female; mean age 44.3 years, range 19.2 – 75.1 years). Primary diagnoses included SCI (n=9), CP (n=7), TBI (n=3), MS (n=1), stroke (n=1), and other (n=3). The mean follow-up was 14.7 years (range, 10.0 – 28.4 years). Outcomes measured included intensity of pain and pain interference (BPI); spasm frequency and severity (PSFS); sleepiness (ESS); fatigue (FSS); quality of life (SWLS, LSQ); and an Intrathecal Baclofen Survey to assess improvements in pain and spasticity, pump and catheter complications, and overall satisfaction.

RESULTS

Spasticity Outcomes: As measured by the PSFS, the mean (SD) spasm frequency was 1.1 ± 0.9 (scale, 0-4) and spasm severity was 1.4 ± 0.7 (scale, 1-3). As measured by the IBS, patients reported a "large" reduction in spasms [mean (SD), 9.4 ± 0.9; scale, 0-10] and a "moderate-to-large" reduction in pain [mean (SD), 8.0 ± 2.4; scale, 0-10]. As measured by the BPI, the mean (SD) pain severity score was 2.6 ± 2.3 (scale, 0-10) and mean pain interference score was 3.3 ± 3.2 (scale, 0-10).

Functional Outcomes: The mean (SD) sleepiness score (ESS) was 7.9 ± 5.4 (scale, 0-24) which represents a "slight chance of dozing" during various activities. The mean (SD) fatigue score (FSS) was 4.1 ± 1.6, representing a neutral score on a scale of 0 to 7 for how fatigue affects various aspects of daily functioning.

Quality of Life Outcomes: The mean (SD) satisfaction with life measure (LSQ) was 3.9 ± 0.9 where a score of 4 represents "rather satisfying". Similarly, the mean (SD) satisfaction score as measured by SWLS was 19.4 ± 8.1 on a scale of 7-35.

Dosing: Mean (SD) dose at the time of the survey was 627.9 ± 306.7 mcg/day.

Adverse Events: Two patients had their pumps removed due to complications. One patient experienced déjà vu episodes; the pump was eventually explanted. The second patient experienced baclofen withdrawal following an infection which had required pump explant. There were a total of 10 catheter changes (0.03 per patient-year).

KEY CONCLUSIONS

Patients receiving ITB therapy for a minimum of 10 years reported low pain and sleepiness levels and high satisfaction levels. Results of the study suggest efficacy and a favorable safety profile in long-term use of ITB therapy.

Limitations: There was a potential selection bias due to limitation of patients with > 10 years of ITB therapy; patients with therapy > 10 years would be expected to demonstrate more positive outcomes. The IBS survey is not a validated survey. The study did not include a control group or baseline measurements.

INTRATHECAL BACLOFEN SURVEY RESULTS

Question	Scale	Mean ±SD	Yes	No
Difficulty keeping pump in good working order	0 – 10[a]	0.8 ± 1.9	-	-
Extent ITB reduced no. of spasms	0 – 10[b]	9.4 ± 0.9	-	-
Extent ITB reduced level of pain	0 – 10[b]	8.0 ± 2.4	-	-
Would undergo pump placement again	Yes/No	-	22 (95.7%)	1 (4.3%)
Would recommend pump to others	Yes/No	-	23 (95.8%)	1 (4.2%)
Overall level of satisfaction with pump	0 – 10[c]	8.8 ± 1.9	-	-
Difficulty with:				
Refilling the pump	Yes/No	-	6 (25.0%)	18 (75.0%)
Making adjustments to pump	Yes/No	-	4 (17.4%)	19 (82.6%)
Becoming physically comfortable w/the pump	Yes/No	-	7 (30.4%)	16 (69.6%)
Mentally adjusting to idea of having a pump	Yes/No	-	6 (27.3%)	16 (72.7%)
Infection of pump or catheter	Yes/No	-	1 (10.0%)	9 (90.0%)
Malfunction and/or early replacement of pump and/or catheter	Yes/No	-	4 (40.0%)	6 (60.0%)

[a] 0 = Very easy, 10 = Very difficult; [b] 0 = No reduction, 10 = Large reduction; [c] 0 = Very unsatisfied, 10 = Very satisfied

Acronyms: Brief Pain Inventory (BPI); Cerebral Palsy (CP); Diener Satisfaction with Life (SWLS); Epworth Sleepiness Scale (ESS); Fatigue Severity Scale (FSS); Intrathecal Baclofen Survey (IBS); Life Satisfaction Questionnaire (LSQ); Multiple Sclerosis (MS); Penn Spasm Frequency Scale (PSFS); Spinal Cord Injury (SCI); Standard Deviation (SD); Traumatic Brain Injury (TBI).

INTRATHECAL BACLOFEN FOR SPASTICITY MANAGEMENT: A COMPARATIVE ANALYSIS OF SPASTICITY OF SPINAL VS CORTICAL ORIGIN [140]

Saval A, Chiodo AE. *J Spinal Cord Med.* 2010;33(1):16-21.

OBJECTIVE

In a retrospective medical chart review, outcome differences between patients with spinal vs. cerebral spasticity were investigated over 3 years in 57 patients treated with ITB therapy for severe spasticity (37 males, 20 females; mean age 47 years, range 19-86 years). Spasticity was due to SCI (n=19; 10 incomplete SCI, 9 complete SCI), MS (n=19), CP (n=7), TBI (n=8), and stroke (n=4).

Patients with spinal spasticity (SCI, MS) were compared to patients with cerebral spasticity (CP, TBI, stroke) for outcomes including daily dose, number of contacts or dose adjustments made by an HCP, infusion mode, adjunct therapy, and types of complications. Differences between MS and non-MS patients were also compared.

RESULTS

Dosing: No group differences in daily dose were observed for spinal vs. cerebral spasticity ($P = 0.729$), though the main effect of time was significant with daily dose increasing over time ($P < 0.001$). The mean (SD) dose for the MS group (227 ± 203 mcg/day) was significantly higher than the dose of the non-MS group (127 ± 67 mcg/day).

Contacts: There were no significant differences in the number of contacts made by an HCP between spinal and cerebral spasticity groups ($P = 0.478$), nor was there a significant change in the number of contacts over time ($P = 0.558$).

Programmed Infusion Mode: There were no significant differences in the infusion mode (flex dosing or simple continuous) programmed for spinal vs. cerebral spasticity at any time point between 3 months and 3 years (3 months, $P = 0.318$; 6 months, $P = 0.605$; 1 year, $P = 0.072$; 2 years, $P = 0.435$; 3 years, $P = 0.392$).

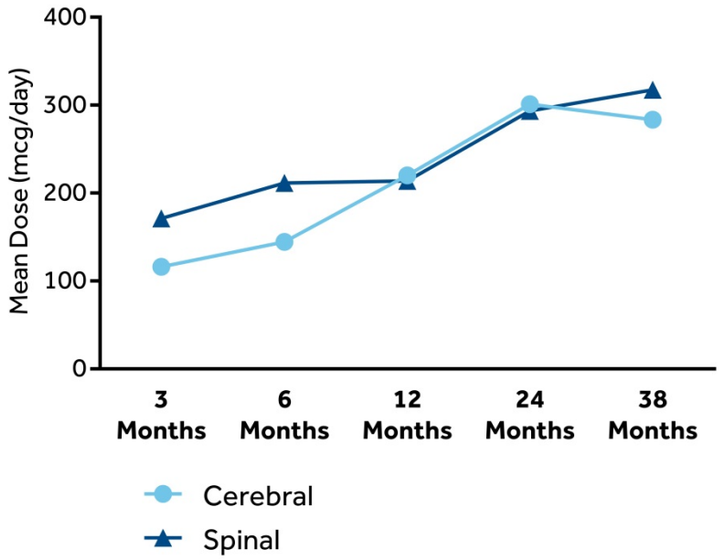
Adverse Events: The overall complication prevalence was 16% over 3 years. There was no statistically significant difference between the spinal and cerebral spasticity groups in complication rate ($P = 0.71$). Within the cerebral spasticity patients, 22% experienced complications; within the spinal spasticity patients, 13% experienced complications. Complications included fractured catheters (n=6), catheter migration (n=2), and pump infection with meningitis (n=1). Subsequent to the pump infection, the patient's catheter was removed and replaced.

KEY CONCLUSIONS

Comparing patients treated with ITB for severe spasticity of cerebral vs. spinal origin, there were no significant differences in daily dose, number of HCP contacts, or the programmed infusion mode. However, patients with MS had a significantly higher mean dose compared to patients without MS. In addition, daily ITB dose increased over time.

Limitations: Attrition and missing data points may have skewed results. Sample sizes were small.

MEAN ITB DOSE



Acronyms: Cerebral Palsy (CP); Healthcare Provider (HCP); Multiple Sclerosis (MS); Spinal Cord Injury (SCI); Standard Deviation (SD); Traumatic Brain Injury (TBI).

A CLINICAL STUDY OF INTRATHECAL BACLOFEN USING A PROGRAMMABLE PUMP FOR INTRACTABLE SPASTICITY [135]

Guillaume D, Van Havenbergh A, Vloeberghs M et al. *Arch Phys Med Rehabil.* 2005;86(11):2165–2171.

OBJECTIVE

A multicenter prospective cohort trial of ITB therapy was conducted in 138 intractable spasticity patients (64% male, 36% female; mean age, 35.2 years, range 4-74 years). Etiology of spasticity included MS (30%), SCI (26%), CP (24%), TBI (7%), stroke (2%), and other (11%). Of the 138 patients enrolled, 136 received an ITB test dose, 133 responded positively to the test dose, and 129 subsequently began ITB therapy. Mean follow-up was 10.8 months (range 1.0-19.2 months). Outcomes measured at baseline, 3, 6, 9, and 12 months post-implant included spasticity severity (AS), spasm frequency (PSFS), pain assessment (NRS), motor and cognitive function (FIM or WeeFIM), patient performance and satisfaction (COPM), and subjective satisfaction ratings.

RESULTS

Spasticity Outcomes: Spasticity severity (AS) was significantly reduced at all follow-ups in upper and lower extremities ($P < 0.001$). Spasm frequency (PSFS) was significantly reduced at 12 months ($P < 0.001$). Pain assessments of worst pain in previous week, least pain in previous week, average pain in the previous week, and current pain at all follow-ups were significantly lower ($P < 0.001$). Worst pain, average pain, and current pain reduced steadily over 12 months whereas least-pain ratings remained stable after the initial reduction.

Functional Outcomes: Motor function (FIM/WeeFIM) significantly improved at 12 months compared to baseline ($P < 0.001$) though not at 3 months. Cognitive function (FIM/WeeFIM) was significantly improved at 3 months compared to baseline ($P = 0.01$) though not at 12 months. The mean combined function score was significantly improved at 3 months ($P = 0.034$) and 12 months ($P < 0.001$) as compared to baseline.

Performance and Satisfaction Outcomes: There were significant improvements at 3 and 12 months in performance and satisfaction in selected COPM occupational tasks ($P < 0.001$ for all). Significant improvements were observed in patient subjective assessments of spasticity and pain relief ($P < 0.001$). Physicians rated overall satisfaction with ITB therapy for each patient, with 87% ratings as good or very good, 8% as fair, and 5% as poor or very poor.

Spasticity relief was rated as good or very good by 6% of patients at baseline, 69% at 3 months, and 84% at 12 months. Similarly, spasticity relief was rated as good or very good by 2% of physicians at baseline and 89% of physicians at 12 months.

Pain relief was rated as good or very good by 12% of patients at baseline and 70% of patients at 12 months. Pain relief was rated as good or very good by 9% of physicians at baseline and 72% of physicians at 12 months.

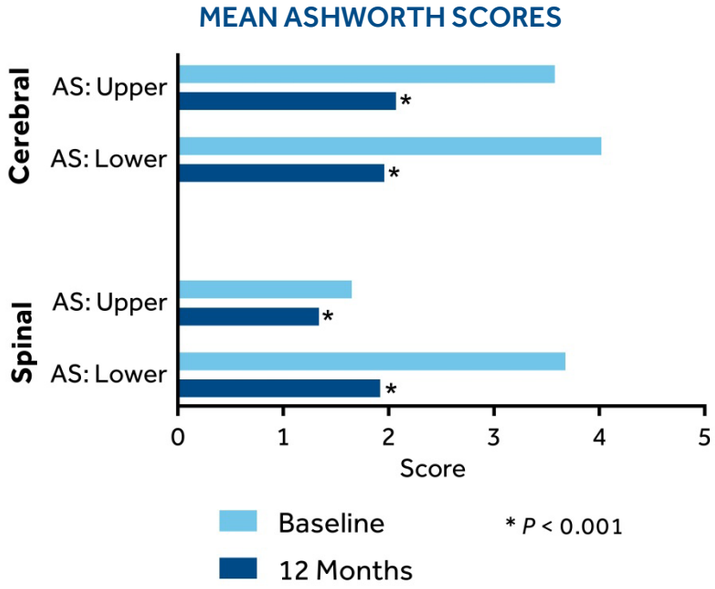
Dosing: Mean ITB dose was 129 mcg/day at implant and 288 mcg/day at 12 months.

Adverse Events: Twelve events were observed in 11 patients prior to implant, of which most were related to the catheter delivering the ITB test dose. Following implant, 55 patients (43%) experienced 92 adverse events; 20% experienced patient-related events, 10% experienced surgery-related events, and 9% experienced catheter-related events. Five deaths occurred among patients with implanted pumps; no deaths were considered to be caused by the pump.

KEY CONCLUSIONS

ITB therapy improved spasticity severity, spasm frequency, pain, and function in patients with severe spasticity. Patients and physicians were satisfied with ITB therapy.

Limitations: The clinical study did not include a separate control group.



Acronyms: Ashworth Scale (AS); Canadian Occupational Performance Measure (COPM); Cerebral Palsy (CP); Functional Independence Measure (FIM); Multiple Sclerosis (MS); Numeric Rating Scale (NRS); Pediatric Functional Independence Measure (WeeFIM); Penn Spasm Frequency Scale (PSFS); Spinal Cord Injury (SCI); Traumatic Brain Injury (TBI).

INTRATHECAL BACLOFEN THERAPY FOR SEVERE SPASTICITY: ANALYSIS ON A SERIES OF 112 CONSECUTIVE PATIENTS AND FUTURE PROSPECTIVES [139]

Natale M, Mirone G, Rotondo M, Moraci A. *Clin Neurol Neurosurg.* 2012;114(4):321–325.

OBJECTIVE

A prospective study of ITB therapy was conducted in 112 patients with severe spasticity (63 males, 49 females; mean age 43.2 years, range 7-63 years). Etiology of spasticity included MS (n=25), CP (n=21), SCI (15), BI (n=22), and other (n=29). Seventy-seven patients were nonambulatory and 35 were ambulatory. Mean follow-up was 55 months (range 12-72 months). Primary outcomes included spasticity severity (MAS) and spasm frequency (PSFS).

RESULTS

Spasticity Outcomes: Spasticity severity (MAS) was reduced from a mean (SD) of 4.5 ± 0.5 prior to implant to 1.2 ± 0.4 at the latest follow-up. Spasm frequency (PSFS) also improved, from a mean (SD) of 3.2 ± 0.4 prior to implant to 0.8 ± 0.2 at the latest follow-up post implant.

Dosing: The mean dose for ITB was 150 mcg/day (range 23 to 500 mcg/day). The effective ITB dose did not correlate with preoperative oral baclofen dose, age, body weight, or gender. ITB dose in ambulatory patients (94 mcg/day) was less than that required for nonambulatory patients (140 mcg/day).

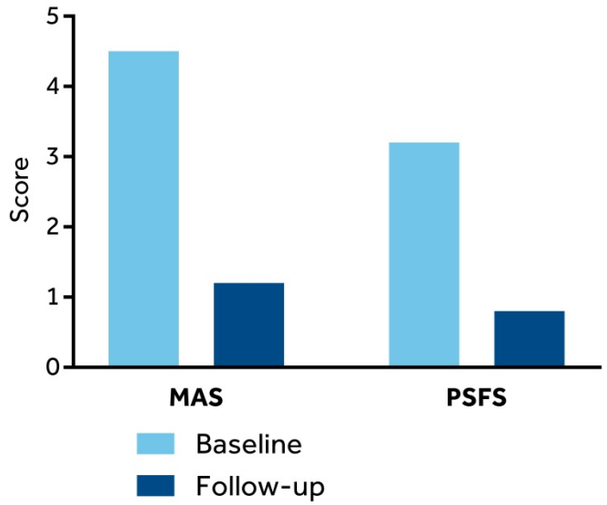
Adverse Events: Seven patients experienced a spinal-type headache during the screening test. Postimplant, drug-induced complications were reported in 7 patients: ITB tolerance (n=4); nausea, dizziness, and drowsiness (n=1); and hypotension and bradycardia (n=2). Ten catheter complications were reported: occlusion and kinks (n=2), breaks (n=3), and dislodgement (n=5). In 2 cases of dislodgement the patients experienced ITB withdrawal syndrome. Pump-related events included 2 pocket infections and 1 skin erosion (mainly due to decubitis). Nine patients were explanted for the following reasons: marked reduction in spasticity (n=3), pocket infection (n=2), skin erosion (n=2), and aesthetic reasons (n=2).

KEY CONCLUSIONS

Spasticity severity and spasm frequency improved with long-term ITB therapy.

Limitations: The study did not include a control group. The authors did not report on statistical significance of spasticity changes. Inconsistencies in reported data were not explained.

MEAN SPASTICITY SCORES



Acronyms: Brain Injury (BI); Cerebral Palsy (CP); Modified Ashworth Scale (MAS); Multiple Sclerosis (MS); Penn Spasm Frequency Scale (PSFS); Spinal Cord Injury (SCI); Standard Deviation (SD).

LONG-TERM OUTCOMES OF CONTINUOUS INTRATHECAL BACLOFEN INFUSION FOR TREATMENT OF SPASTICITY: A PROSPECTIVE MULTICENTER FOLLOW-UP STUDY[130]

Delhaas EM, Beersen N, Redekop WK, Klazinga NS. *Neuromodulation*. 2008;11(3):227–236

OBJECTIVE

A prospective, multicenter study of long-term ITB therapy was conducted in 115 patients with severe generalized spasticity. Etiology of spasticity included MS (n=51), SCI (n=30), CP (n=12), TBI (n=5), stroke (n=3), and other (n=14). Of the 115 patients who completed intake for the study, 110 met screening criteria and 74 were implanted. Data was collected prior to implant, after screening, and at 1, 3, 6, 9 and 12 months postimplant. Outcome measures were spasticity severity (AS), spasm frequency (SFS), clonus (CS), health-related functional condition (SIP-68), disabilities in daily life (FIM), health-related quality of life (EQ-5D), and a measure of problems that patients and caregivers wanted resolved with ITB therapy (PPRS).

RESULTS

Spasticity Outcomes: All 3 spasticity measures (AS, SFS, CS) significantly improved at every visit as compared to baseline, with the exception of clonus at 12 month follow-up.

Functional Outcomes:

- No significant changes were observed in SIP-68 scores at 6 or 12 months. Subscale analysis found improvements in social behavior ($P = 0.025$), emotional stability ($P = 0.022$), and mobility range ($P = 0.045$).
- There were no significant improvements in functional gain (FIM) at 6 or 12 months. In subscale analysis, the only significant improvements were seen at 6 months in locomotion ($P = 0.046$) and walk/wheelchair ($P = 0.007$). No subscales showed significant improvement at 12 months.
- The self-reported PPRS scores were significantly improved at all follow-ups compared to baseline ($P < 0.001$). When the MS and SCI subgroups were analyzed separately, PPRS scores also significantly improved.

Quality of Life Outcomes: Health-related quality of life (QoL) significantly improved at 6 months ($P = 0.04$) but not 12 months. EQ-5D VAS scores were significantly improved at 6 months ($P < 0.05$) and 12 months ($P < 0.05$) as compared to baseline.

Dosing: The mean ITB dose was 106.9 mcg/day (range 50 to 200 mcg/day) at implant, increasing to 161.6 mcg/day (range 0 to 995.9 mcg/day) at discharge and to 239.6 mcg/day (range 70 to 825.9 mcg/day) at 12 months. The dose escalated initially and stabilized after 6 months.

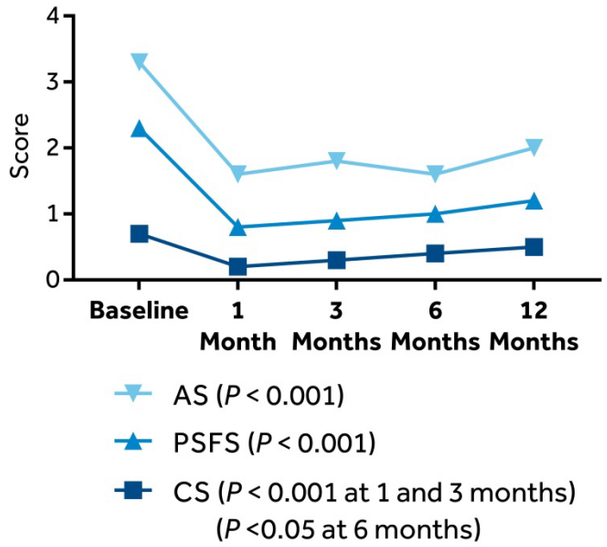
Adverse Events: A total of 64 adverse events were reported; 18 were minor, 41 moderate, and 5 serious. Eight events occurred during screening (CSF leakage, postpuncture syndrome) and 56 after implant. Thirty-five reoperations were performed, including catheter-only replacement (n=20), catheter repositioning (n=4), catheter and pump replacement (n=2), pump repositioning (n=3), and pump and catheter explant (n=6). There were 14 deaths, none related to ITB therapy.

KEY CONCLUSIONS

Spasticity severity, spasm frequency, and severity of self-reported problems significantly improved with ITB therapy.

Limitations: The study did not include a control group and was not powered to find meaningful differences within the MS and SCI subgroups. A significant number of potential patients dropped out prior to implant. The attrition rate was fairly high following implant which may impact generalizability of the results. The PPRS is not a validated tool.

MEAN SPASTICITY SCORES



Acronyms: Ashworth Scale (AS); Cerebral Palsy (CP); Cerebrospinal Fluid (CSF); Clonus Scale (CS); EuroQol five dimensions questionnaire (EQ-5D); Functional Independence Measure (FIM); Multiple Sclerosis (MS); Personal Problems Rating Scale (PPRS); Quality of Life (QoL); Sickness Impact Profile-68 (SIP-68); Spasm Frequency Scale (SFS); Spinal Cord Injury (SCI); Traumatic Brain Injury (TBI); VAS (Visual Analog Scale).

RATE OF COMPLICATIONS AMONG THE RECIPIENTS OF INTRATHECAL BACLOFEN PUMP IN JAPAN: A MULTICENTER STUDY [143]

Taira T, Ueta T, Katayama Y et al. *Neuromodulation*. 2013;16(3):266-272.

OBJECTIVE

A multicenter study in Japan evaluated complication rates of ITB therapy in 400 patients with severe spasticity (277 males, 123 females; mean age 47.2 years, range 9 to < 90 years). Etiology of spasticity included SCI (n=91), MS (n=9), CP (n=48), TBI (n=33), other spinal origin (n=123), other cerebral origin (n=90), cerebral and spinal origin (n=5), and unknown (n=1). A minimum follow-up of 1 year was accomplished in 78.3% of patients.

RESULTS

Adverse Events: Adverse events were observed in 148 patients; 93 of the events were severe. Catheter complications were observed in 34 patients and there were 7 pump-related complications. Nine patients experienced a mild ITB overdose. There were 12 infections reported, of which 9 required surgical intervention. Seven of the 13 patients experiencing CSF leak required surgical intervention. There were no reports of ITB withdrawal symptoms.

Deaths: Eighteen deaths were reported due to: pneumonia (n=6), suicide (n=3), sepsis/multiorgan failure (n=3), cerebral hemorrhage (n=2), tracheal bleeding (n=1), myocardial infarction (n=1), and unknown (n=2). No deaths were attributed to ITB therapy or surgical procedures.

Dosing: The mean ITB dose was 172 mcg/day (range 23 to 1412 mcg/day).

KEY CONCLUSIONS

In a large multicenter study, complication and infection rates were low. The most common complication related to ITB therapy was catheter migration in 6.3% of patients.

CATHETER, PUMP, AND PROCEDURE-RELATED ADVERSE EVENTS

Type of Complication	Total No. of Events	No. of Events Considered Severe
Catheter-related	34 patients (8.5%)	30 patients (7.5%)
Migration	25 (6.3)	23 (5.8)
Dislodgement	1 (0.3)	1 (0.3)
Kinking	1 (0.3)	1 (0.3)
Breakage	6 (1.5)	5 (1.3)
Obstruction	2 (0.5)	1 (0.3)
Pump-related	7 patients (1.8%)	4 patients (1.0%)
Rotation	1 (0.3)	0
Alarm abnormality	1 (0.3)	0
Memory error	1 (0.3)	0
Delayed recovery	1 (0.3)	1 (0.3)
Pump malfunction	1 (0.3)	1 (0.3)
Abnormal infusion rate	2 (0.5)	2 (0.5)
Surgical Procedure-related	24 patients (6.0%)	16 patients (4.0%)
Infection	12 (3.0)	9 (2.3)
CSF leak	13 (3.0)	7 (1.8)

Acronyms: Cerebral Palsy (CP); Multiple Sclerosis (MS); Spinal Cord Injury (SCI); Traumatic Brain Injury (TBI).

INCIDENCE AND IDENTIFICATION OF INTRATHECAL BACLOFEN CATHETER MALFUNCTION [132]

Dvorak EM, McGuire JR, Nelson ME. *PM R.*2010;2(8):751-756.

OBJECTIVE

A retrospective chart review of 167 ITB patients (100 males, 67 females; age at implant mean age 39.3 years, range 8.3-69.9 years) was conducted to identify cases of pump and catheter malfunction. Patient diagnoses included SCI (n=55), CP (n=37), MS (n=31), TBI (n=19), stroke (n=7), other BI (n=3), and other (n=15). Mean follow-up time with ITB therapy was 4.6 years (range 0.04-14.9 years).

RESULTS

Adverse Events: There was an overall 22.2% complication rate with ITB therapy, consistent with prior publications.

- Thirty-seven pump or catheter malfunctions were identified in 33 patients. Four patients had 2 complications and 29 patients had 1 complication.
- There was no significant correlation between patient diagnosis and complication rate.
- Complications did not include pumps replaced due to end of battery life or pump or catheter replacements due to infection.

Diagnostic Testing: Most malfunctions were identified using plain radiography or fluoroscopy/computed tomography.

- Radiographs identified 35.1% of all system malfunctions. All catheter fractures and dislodgements, and large pump-catheter disconnections, were visualized on radiographs.
- An additional 48.6% of malfunctions were identified using fluoroscopy/computed tomography, which were able to visualize lack of CSF return, abnormal contrast, and subdural catheter placement.

KEY CONCLUSIONS

In a retrospective chart review, the rate of catheter/pump malfunctions with ITB therapy was found to be similar to other studies. Catheter complications were more common than pump complications.

All patients who had system complications requested a replacement because of satisfaction with ITB therapy in reducing their spasticity.

ITB THERAPY PUMP AND CATHETER COMPLICATIONS

Type of Complication	No. of Events
Catheter kink/obstruction	14 (37.8)
Catheter disconnection	7 (18.9%)
Subdural catheter placement	7 (18.9%)
Catheter fracture	4 (10.8%)
Catheter dislodgement	4 (10.8%)
Pump failure	1 (2.7%)

Acronyms: Brain Injury (BI); Cerebral Palsy (CP); Multiple Sclerosis (MS); Spinal Cord Injury (SCI); Traumatic Brain Injury (TBI).

OCCURRENCE OF ADVERSE EVENTS IN LONG-TERM INTRATHECAL BACLOFEN INFUSION: A 1-YEAR FOLLOW-UP STUDY OF 158 ADULTS [128]

Borrini L, Bensmail D, Thiebaut JB et al. *Arch Phys Med Rehabil.* 2014;95(6):1032-1038.

OBJECTIVE

A prospective, observational cohort study of 158 patients (102 males, 56 females; mean age 45.7 years, range 17-87 years) assessed adverse events associated with ITB therapy. The 1 year study included 128 non-surgical patients (previously implanted for ITB who did not need a replacement), 10 surgical patients (previously implanted who had replacement pumps implanted during the study period), and 20 newly implanted surgical patients. Etiology of spasticity included SCI (n=67), MS (n=45), CP (n=22), stroke (n=8), TBI (n=3), and other (n=13). Median follow-up was 10.5 months and 123 (78%) patients were followed through the entire 1 year study period. AEs were analyzed for age, ambulatory status, spinal vs. cerebral spasticity, surgical status, and ITB therapy duration.

RESULTS

Adverse Events: A total of 38 AEs were reported in 28 patients (17.7%). AEs were categorized as procedure-related (53%), device-related (29%), or drug-related (18%). The global incidence rate was 0.023 AEs and 0.011 serious AEs per month of ITB therapy. Serious AEs extended hospital stays by a mean of 16 days (range 5-60 days). No deaths or permanent sequelae resulted from the AEs related to ITB therapy.

- Surgical (new or replacement) patients were significantly more likely to experience an AE than non-surgical patients ($P = 0.04$)
- Factors which did not have a significant impact on the frequency of AEs included: ambulatory status, spinal vs. cerebral origin, age, daily dose, and duration of ITB therapy during follow-up.

KEY CONCLUSIONS

A relatively low complication rate was observed, More than half of the AEs were related to the surgical procedure.

Limitations: The study evaluated AEs during pump implant and follow-up, and did not include any that may have occurred during a screening trial of ITB therapy.

PROCEDURE-RELATED ADVERSE EVENTS

Type of Adverse Event	Total No. of Events	No. of Events Considered Serious
Scar complications	2	1
Scar dehiscence	1	1
Neuroma	1	0
Pump pocket hematoma	4	1
CSF collection	2	0
Infection	10	3
Pump pocket infection	1	1
Urinary tract infection	8	1
Aspiration pneumonia	1	1
Other	2	0
Bowel obstruction	1	0
Post-lumbar puncture headache	1	0
Total	20 (53%)	5 (13%)

DEVICE-RELATED ADVERSE EVENTS

Type of Adverse Event	Total No. of Events	No. of Events Considered Serious
Catheter complications	9	9
Migration	4	4
Disconnection	1	1
Dysfunction of unknown origin	4	4
Pump dysfunction	1	1
Pressure ulcer against pump	1	1
Total	11 (29%)	11 (29%)

DRUG-RELATED ADVERSE EVENTS

Type of Adverse Event	Total No. of Events	No. of Events Considered Serious
Long-term baclofen AE	6	1
Bloating-constipation	4	1
Dysuria	1	0
Erectile dysfunction	1	0
Pharmacologic event (withdrawal)	1	1
Total	7 (18%)	2 (5%)

Acronyms: Adverse Events (AE); Brain Injury (BI); Cerebral Palsy (CP); Cerebrospinal Fluid (CSF); Multiple Sclerosis (MS); Spinal Cord Injury (SCI).

COMPLICATIONS OF INTRATHECAL BACLOFEN PUMPS IN CHILDREN [133]

Gooch JL, Oberg WA, Grams B et al. *Pediatr Neurosurg.* 2003; 39(1):1-6.

OBJECTIVE

A retrospective chart review evaluated device and major non-device complications in 100 children receiving ITB therapy due to severe spasticity (mean age at pump placement 11.2 years, range 3.7-21 years). Etiology of spasticity included CP (n=76), TBI (n=11), SCI (n=2), and other (n=11). Half of the patients (n=50) were at GMFCS level V, 35 at GMFCS level IV, 7 at GMFCS level III, and 8 at GMFCS level II. During the study period 117 pumps were implanted in the 100 patients. Sixty-two pumps had a catheter access port and 55 did not. Fifty pumps were connected to 1-piece catheters and 67 to 2-piece catheters. Minor dosage-related adverse effects such as drowsiness or weakness in the trunk or lower limbs were not included. Follow-up ranged from 6 months to 5.6 years.

RESULTS

Adverse Events: Forty-eight complications were reported in 24 patients (24%). Eleven patients experienced just one event and 13 experienced more than one event. Forty-three of the complications were device related and 5 were non-device related. Time to detection of first device-related complication averaged 262 days (range 7-807 days).

- Catheter disconnection was the most frequent complication with 11 occurrences. Significantly more disconnections occurred in pumps with a catheter access port (10/62) than in pumps without a catheter access port (1/55) ($P = 0.02$). There was not a significant difference in the frequency of catheter disconnections in pumps with 2-piece catheters compared to those with 1-piece catheters.
- Catheter dislodgement was the second most frequent complication with 10 occurrences. While a slightly higher percentage of pumps with catheter access ports (8/62) had a catheter dislodgement compared to those pumps without a catheter access port (2/55), the difference was not statistically significant. However, the frequency of catheter dislodgements in pumps with a 1-piece catheter (7/50) was significantly higher than in pumps with a 2-piece catheter (3/61) ($P = 0.05$).

KEY CONCLUSIONS

Device-related and major non-device complications occurred in 24% of pediatric patients receiving ITB therapy. The most frequent complications were catheter disconnection and catheter dislodgement.

Limitations: Pumps included in the study were SynchroMed and SynchroMed EL models. No SynchroMed II models were included. Effect of catheter access port on complication rates may not reflect expected performance with SynchroMed II. The reported number of pumps with and without catheter access ports is inconsistent within the paper.

DEVICE-RELATED COMPLICATIONS

Type of Complication	No. of Events
Catheter disconnection	11
Catheter dislodgement	10
Pump infection	5
CSF leak (persistent)	4
Catheter kink	4
Catheter tear	3
Catheter access port defect	2
Pump flipped	2
CSF leak with infection	1
Pump failure	1
Total	43 (90%)

MAJOR NON-DEVICE-RELATED COMPLICATIONS

Type of Complication	No. of Events
Mental status decline	2
Bradycardia	1
Severe spasms	1
Overdose	1
Total	5 (10%)

Acronyms: Cerebral Palsy (CP); Gross Motor Function Classification Scale (GMFCS); Spinal Cord Injury (SCI); Traumatic Brain Injury (TBI).

ANALYSIS OF COMPLICATIONS IN 430 CONSECUTIVE PEDIATRIC PATIENTS TREATED WITH INTRATHECAL BACLOFEN THERAPY: 14-YEAR EXPERIENCE [138]

Motta F, Antonello CE. *J Neurosurg Pediatr*. 2014;13(3):301-306.

OBJECTIVE

A retrospective chart review evaluated safety and complications of ITB therapy at a children's hospital in Italy. These authors had previously reported safety and complications for ITB therapy in 200 patients implanted between 1998 and 2004 (Motta et al 2007). This chart review included 430 patients who received ITB therapy from 1998 to 2012. The mean age at implant was 13.3 years, with a mean follow-up period of 8.6 years. Patients had severe spasticity due to CP (n=383), SCI or BI (n=15), MS (n=1), or other causes (n=31).

RESULTS

One or more complications occurred in 25% of patients. Major complications, defined as those that required a surgical intervention, were infections, CSF leaks, and device problems related to the catheter or pump.

Thirty of the 40 patients with infection were explanted. The infection rate was significantly less using subfascial vs. subcutaneous pump placement (3.6% of all subfascial implants vs. 20.1% of all subcutaneous implants, respectively; $P < 0.001$).

Twenty-one patients had CSF leaks that required treatment with a blood patch. Explant was needed in 3 cases due to chronic CSF leak. In 2005 the center started applying a pressure dressing that led to spontaneous resolution of CSF leaks, with fluid aspiration required in only a few cases.

The majority of catheter complications were resolved with replacement (n=61, 94%).

KEY CONCLUSIONS

Surgical technique and patient management were observed to reduce ITB therapy complications. Most events occurred within the first 12 months of implant. Although 37.5% of all explanted devices were removed at the request of the patient or caregiver, the majority of parents and patients were satisfied with ITB therapy.

MAJOR DEVICE AND PROCEDURE-RELATED COMPLICATIONS

Type of Complication	No. of Patients
Device-related	
Pump flipped	3 (0.7%)
Pump migration to intraperitoneal cavity	1 (0.2%)
Catheter migration, disconnection, or breakage	65 (15%)
Device explanted due to supposed device problems	2 (0.4%)
Device explanted for unknown reasons	10 (2%)
Device explanted at patient/parent request	27 (6%)
Procedure-related	
Infection at pump pocket site	40 (9%)
Device explanted due to infection	30/40 (75%)
CSF leak*	62 (14%)
Requiring 1 or more blood patch	21/62 (34%)
Resolved spontaneously	38/62 (61%)
Device explanted due to chronic leakage	3/62 (5%)

*In 2005 the center started applying a pressure dressing that lead to spontaneous resolution of CSF leaks, with fluid aspiration required in only a few cases.

Acronyms: Brain Injury (BI); Cerebral Palsy (CP); Cerebrospinal Fluid (CSF); Multiple Sclerosis (MS); Spinal Cord Injury (SCI).

IDENTIFICATION AND MANAGEMENT OF INTRATHECAL BACLOFEN PUMP COMPLICATIONS: A COMPARISON OF PEDIATRIC AND ADULT PATIENTS [145]

Vender JR, Hester S, Waller JL et al. *J Neurosurg Pediatr*. 2006;104:9-15.

OBJECTIVE

A retrospective study reviewed 314 pump and intrathecal catheter placement procedures completed during 5 years at a single institution in the U.S. Postoperative ITB therapy complications were analyzed for 226 pediatric and 88 adult procedures performed in 116 pediatric and 55 adult patients, most with CP. The authors reported complications that required repeat surgical procedures, complications that did not require a surgical intervention, and cases of elective surgical procedures. Complications occurred in 45 pediatric and 12 adult patients.

RESULTS

- **Catheter-related:** Most complications for pediatric and adult patients were catheter-related, which included hub fracture or dislocation, breakage or disruption, occlusion, and slippage or pullout. Catheter problems typically presented with symptoms of ITB underdose or withdrawal, or a loss of therapeutic effect that was not responsive to escalating doses.
- **Pump-related:** Pump flipping only happened in pediatric patients with oversized subfascial pump pockets. Both cases of flipped pumps had related catheter complications. Of 5 pump malfunctions requiring explant, 2 were intrinsic due to a stopped rotor (n=1) and battery failure without a low battery alarm (n=1).
- **Wound-related:** Wound-related complications occurred more frequently in pediatric patients (46%) than adults (25%). Most pseudomeningoceles that occurred more than 2 weeks after catheter implant were due to fractured or migrated catheters. Pediatric patients were more susceptible to CSF fistulas than adult patients, thought to be related to their decreased amount of muscle and subcutaneous tissue and less resistance to pseudomeningocele formation or wound breakdown. The authors attempted to salvage pump infections in pediatric cases, even if a deep pocket infection was present; but 13 of 14 pediatric patients with infection who were treated with antibiotics eventually required explant.

KEY CONCLUSIONS

The pediatric group had a significantly higher overall number of complication-related procedures. Careful technique, close observation, and aggressive evaluation and correction of problems can reduce the incidence and severity of complications.

Type of Complication	Pediatric cases	Infection rate	Adult cases	Infection rate
Repeat procedure required	**80**		**16**	
Pump	5		2	
Pump malfunction requiring explant	3	66.67	2	0
Pump rotation/flipping	2	0	0	0
Catheter	38		10	
Catheter hub fracture/dislocation	12	10	3	0
Catheter breakage/disruption	3	0	2	0
Catheter occlusion	9	22.22	2	50
Catheter slippage/pullout	14	8.33	3	33.33
Wound	37		4	
CSF leak/fistula	7	50	1	100
Pseudomeningocele	7	28.57	0	0
Wound dehiscence	1	0	0	0
Infection: explant despite antibiotic therapy	13	NA	2	NA
Infection: explant, no antibiotic therapy	7	NA	1	NA
Infection: salvage after antibiotic therapy	1	NA	0	NA
Debridement of granuloma	1	100	0	0
No surgery or antibiotics required	**3**		**5**	
Chemical meningitis	1		0	
Suboccipital pain	0		3	
Drug overdose	2		1	
Drug withdrawal	0		1	
Elective repeat procedures	**146**		**72**	
New pump implant	116	1.29	55	0
Reposition pump	3	0	2	0
Catheter reposition/advancement	10	20	4	0
Elective pump replacement, EOL	15	0	11	0
Exploration of catheter w/normal function	2	50	0	0

Acronyms: Cerebral Palsy (CP); Cerebrospinal Fluid (CSF); End of Battery Life (EOL).

INFECTIOUS COMPLICATIONS OF INTRATHECAL BACLOFEN PUMP DEVICES IN A PEDIATRIC POPULATION [131]

Dickey MP, Rice M, Kinnett DG et al. *Pediatr Infect Dis J*. 2013; 32(7): 715-722.

OBJECTIVE

A retrospective study of patients receiving ITB therapy reviewed the proportion of patients with infectious and noninfectious complications, assessed risk factors for infection, and described clinical presentation, management, and outcome of infections. The study included 139 pediatric patients (mean age at implant 13.6 years) with severe spasticity CP (n=115), traumatic or anoxic BI (n=16), SCI (n=2), or other causes (n=6). The patients were implanted with an ITB pump between December 1996 and December 2010, and all but 2 patients had at least 1 year of follow-up data.

RESULTS

Infectious and Noninfectious Complications

During the first year of ITB therapy, 24 patients (17%) had an infectious or noninfectious complication requiring at least 1 secondary procedure. Catheter malfunctions were the most common complication (8%) followed by pump failures/replacements (6%). Seven patients (5%) developed an infection after initial pump placement, most occurring within 30 days of primary pump implant. The median time to infection was 14 days (mean 33 ± 42 days). Some patients experienced drug-related complications of overdose (4%) and withdrawal (1%), which resolved without surgical intervention.

In 15 years of follow-up, 24 patients had 27 infections of superficial (22%), deep (33%), or organ space (45%) location. Most infections (96%) were treated with oral and/or intravenous antimicrobial therapy. Antimicrobial therapy was successful in 41% of patients with infection. In addition to antimicrobial therapy, pump and pocket disinfection was attempted in 4 of 9 deep infections and 3 of 12 organ space infections, but 5 pumps could not be salvaged and the patients were explanted. The need to explant differed based on the type of infection ($P = 0.004$).

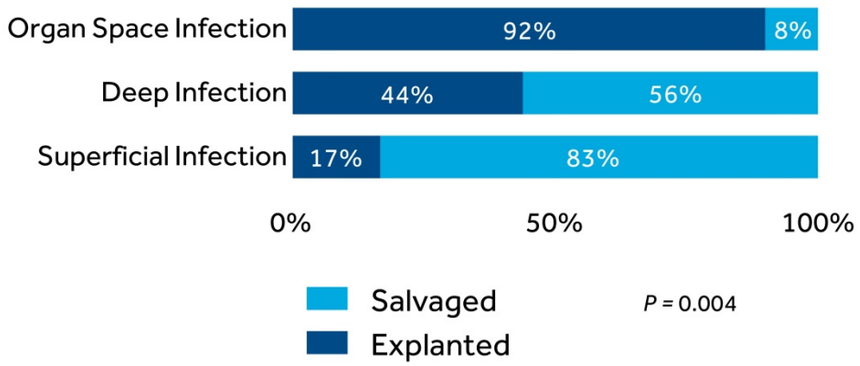
Risk Factors for Infection

Patients with infection were more likely to have spasticity secondary to brain injury, spinal cord injury, or genetic disorders as compared to patients with CP (86% compared to 14%, $P < 0.0001$). Patient gender, age, weight, and site of pump implant (subcutaneous or subfascial) were not correlated to infection. There was no significant difference in infection location (superficial, deep, or organ space) in patients with initial pump placement versus subsequent secondary procedures.

KEY CONCLUSIONS

Infectious complications with ITB therapy in a pediatric population were relatively uncommon, but 59% of all infections required explant. Deep and organ space infections were more difficult to resolve than superficial infections. They often required intravenous antimicrobials in addition to pump explant to fully resolve the infection.

EXPLANT RATE BY INFECTION TYPE



Acronyms: Brain Injury (BI); Cerebral Palsy (CP); Spinal Cord Injury (SCI).

INTRATHECAL BACLOFEN THERAPY: COMPLICATION AVOIDANCE AND MANAGEMENT [136]

Haranhalli N, Anand D, Wisoff JH et al. *Child's Nerv Sys*. 2011;27(3):421-427.

OBJECTIVE

Surgical technique, complication types, and complication timing were collected in a retrospective chart review of 87 patients (age range 5-27 years) treated with ITB therapy for severe spasticity due to CP (n=61), BI (n=6), or other etiology (n=20). All patients underwent complication-related procedures at a single US institution between July 1998 and December 2008, but 11 patients were initially implanted and managed elsewhere.

RESULTS

In the group of 76 patients implanted and managed at the institution, 13 patients experienced 25 complications. The mean time to first complication after pump implant was 24.2 months. Seventeen of 25 complications in this group were considered preventable. In the group of 11 patients initially implanted and managed elsewhere, 4 patients experienced 6 complications that were treated at the institution. None of these complications were considered preventable.

KEY CONCLUSIONS

Analysis of complications requiring surgical intervention revealed preventative methods that can be taken to reduce the risk of such complications. These complications included catheter migration or disconnection, equipment protrusion, CSF leaks, and infection. Preventative methods included stricter patient selection, more emphasis on postoperative care, and alternate surgical techniques for catheter and pump implant.

COMPLICATIONS REQUIRING SURGICAL INTERVENTION

Type of Complication	No. of Patients
Catheter fracture	11
Subcutaneous fluid collection	5
Lumbar wound/CSF infection	3
Lumbar catheter/connector protrusion	3
Pump malfunction	3
Distal catheter migration	2
Catheter disconnection	1
Catheter flipping	1
Baclofen withdrawal	1
Idiopathic system malfunction	1

Acronyms: Brain Injury (BI); Cerebral Palsy (CP); Cerebrospinal Fluid (CSF).

GLOSSARY

TERM	DEFINITION
Acquired Brain Injury (ABI) or Brain Injury (BI)	Brain injury is an inclusive term for damage to the brain that occurs after birth and is not related to a hereditary, congenital, or degenerative disease. Traumatic brain injury, hypoxic and anoxic brain injury, and stroke are forms of acquired brain injuries.
Ashworth Scale / Modified Ashworth Scale	The Ashworth Scale tests resistance to passive movement around a joint with varying degrees of velocity. Scores range from 0-4, with 0 indicating no resistance and 4 indicating rigidity. The Modified Ashworth Scale is similar, but adds a +1 score used to indicate resistance throughout less than half of the range of movement.
Baclofen	Drug that inhibits the release of excitatory neurotransmitters, inhibiting spastic response to stretch reflex.
Barthel Index	The Barthel Index is an ordinal scale used to measure the ability of an individual with a neuromuscular or musculoskeletal disorder to care for him/herself and perform activities of daily living. It assesses 10 activities of daily living and mobility activities rated by the amount of assistance required to complete: feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation, and stair climbing. See also: Functional Independence Measure
Caregiver Questionnaire	A CP-specific health-related quality of life questionnaire that measures caregivers' difficulties and satisfaction in four dimensions: personal care, positioning/transfers, comfort, and interaction/communication. Negative change represents improvement.
Cerebral palsy (CP)	Cerebral palsy is a nonprogressive neurological disorder due to brain injury or malformation early in life. It is a group of permanent early childhood movement disorders. Motor symptoms may include spasticity.
Center for Epidemiologic Studies Depression Scale (CES-D)	The CES-D is a caregiver self-assessment that rates symptoms of depression. It measures 20 items on a scale of 0 to 3, with 0 indicating rarely or none of the time and 3 indicating most or almost all the time.
Child Health Questionnaire ™ Parent Form (CHQ-PF50)	The CHQ-PF50 is a standardized quality of life questionnaire designed for children of 5-18 years of age. It measures 14 individual health concepts and can be aggregated into 2 summary component scores for physical functioning and psychosocial health on a 0-100 scale.
Contracture	Permanent shortening of a muscle due to prolonged spasticity.
Conventional Medical Management (CMM)	A nonsurgical spasticity treatment protocol that may include physical and occupational therapy, orthotics, mobility aids, oral medications, and chemodenervation. CMM does not include ITB therapy, neurosurgery, or orthopedic surgery.
Deep tendon reflex measurement	A rubber hammer or other object is lightly tapped on a tendon at a joint. Taps are usually repeated multiple times, then scored and averaged. Zero is typically absent reflex, 2 is normal reflex, and 5 is sustained clonus, although some deep tendon reflex scales may use 0 to 4.
Epworth Sleepiness Scale (ESS)	The ESS is a patient self-administered questionnaire that measures general level of daytime sleepiness or average sleep propensity in daily life.
EQ-5D	The EQ-5D is a non-disease-specific patient self-assessment questionnaire that measures health-related quality of life.
Fatigue Severity Scale (FSS)	The FSS is a patient self-assessment that measures fatigue severity and how it interferes with activities of daily living.
Ferrans and Powers Quality of Life Index (QLI)	The QLI is designed to measure quality of life overall and in 4 domains (health and functioning, psychological/spiritual, social/economic, and family). Its ratings measure subjective well-being by assessing satisfaction with these domains of life, based on the relative importance to the patient. There is not enough data to confirm that this tool is sensitive enough to measure the relationship between quality of life and spasticity.
Functional Assessment Measure (FAM)	The FAM is a 12-item adjunct tool to the FIM, and addresses functional areas that the FIM does not emphasize including cognitive, behavioral, communication, and community functioning.

TERM	DEFINITION
Functional Independence Measure (FIM)	The FIM is an 18-item tool used in an inpatient rehabilitation setting to measure the severity of disability and need for assistance in carrying out activities of daily living. Tasks are rated on a 7-point ordinal scale from total assistance/complete dependence to complete independence. A higher score indicates higher level of function. The FIM's 18 items are categorized into 6 motor and cognitive subscales.
Gamma-aminobutyric acid (GABA)	A major inhibitory neurotransmitter in the central nervous system, which controls synaptic transmission and inhibits the excitability of neurons to which it binds.
GABA receptor agonist	A drug that binds to and stimulates GABA receptors, increasing their inhibitory activity.
Gillette Functional Assessment Questionnaire (Gillette FAQ)	The Gillette FAQ is a self-reported questionnaire that includes a 10-level ambulatory function classification (FAQ Walking Scale) and a 22-item functional locomotor activity classification on a 5-point Likert Scale (FAQ 22-item skill set). It focuses on what the patient can accomplish individually with assistive devices. A higher score indicates higher functional abilities.
Gillette Gait Index (GGI)	The GGI is calculated from computerized gait analysis and measures gait abnormalities within 16 kinematic and temporal parameters. It quantifies the amount that gait deviates from normal. Higher value represents more severe gait abnormality. It has been validated in children with CP.
Gross Motor Function Measure (GMFM)	The GMFM is a standardized clinical tool that evaluates change over time in five dimensions of motor function ability in children aged 5 months to 16 years with CP: lying and rolling, sitting, crawling and kneeling, standing and walking, and running and jumping. It uses a 4-point score for each item, summed to calculate raw and percent scores for each dimension and overall score.
Gross Motor Function Classification System (GMFCS)	The GMFCS is a 5-level classification of the ability of children with CP to initiate movement, with an emphasis on sitting, transfers, and self-mobility. Levels are based on functional abilities and limitations, need for assistive technology such as walkers or wheelchairs, and to a lesser degree, the quality of movement. A higher level indicates more severe limitations.

TERM	DEFINITION
Hypertonia	Condition of increased tightness of muscle tone and reduced capacity of the muscle to stretch, resulting in increased rigidity, tension, and spasticity of the muscles.
Incremental cost-effectiveness ratio (ICER)	ICER is a ratio of change in costs to change in effects (e.g., quality-adjusted life year).
ITB Therapy Titration Phase	The first 60 days or so after pump implant. The goal of titration is a stable dose that provides optimal therapeutic response and meets the patient's goals for function, comfort, and ease of care. During the titration phase the patient is monitored and dose adjusted for response to ITB, and weaned from oral antispasticity medications if this was not done before the implant procedure.
ITB Therapy Maintenance Phase	Once optimal dose is reached through titration, the patient continues to be seen for spasticity evaluation, patient education, pump refills and checks, and dose adjustments.
Investigational Device Exemption (IDE)	An IDE allows an investigational device to be used in clinical studies to collect safety and efficacy data in support of a premarket approval (PMA) application submission to the U.S. FDA.
Investigational New Drug (IND)	An IND provides authorization for an investigational drug or biological to be administered to humans. It also provides permission for a drug sponsor to ship drug across state lines to clinical investigators before a marketing application has been approved by the U.S. FDA. IND applications are required for clinical studies for new indications, changes in approved route of administration or dose, change in approved patient population, and any significant change in approved drug promotion.
Intrathecal (subarachnoid) space	The space containing cerebrospinal fluid (CSF) between the arachnoid mater and pia mater of the spinal cord.
Intrathecal baclofen (ITB)	Delivery of baclofen directly into the intrathecal space by lumbar puncture or an indwelling intrathecal catheter connected to a drug delivery pump.

TERM	DEFINITION
Impact on Family Scale	The Impact of Family Scale is a caregiver self-assessment that measures the impact of pediatric illness on the family.
Lifestyle Assessment Questionnaire	A questionnaire that measures the impact of childhood disability on patients and their families. It contains 6 dimensions for physical independence, clinical burden, mobility, schooling, economic burden, and social integration. Negative change represents a lower impact of disability.
Life Orientation Test (LOT)	The LOT is an assessment of generalized optimism vs. pessimism.
Lovett Scale	The Lovett scale is used to determine functional level and strength of muscle. Scores range from 0-5, signifying no evidence of contractility (0) to full range of motion against gravity with full resistance (normal, 5).
Manual Muscle Test (MMT)	The MMT is a standardized assessment of muscle strength. Scores range from 0-5, with 0 indicating no muscle contraction and 5 indicating normal range of motion.
Monte Carlo Simulation	A Monte Carlo simulation is a probabilistic technique to address uncertainty and variability in cost modeling studies. It accounts for variability and randomness in patient characteristics and treatment outcomes that cannot be addressed mathematically.
Motor Activity Log (MAL)	The MAL is a patient self-assessment of quality and amount of movement during common activities of daily living.
Multiple sclerosis (MS)	Multiple sclerosis is an immune-mediated progressive disease that destroys the myelin membrane of nerves in the brain and spinal cord. Demyelination impedes neuronal communication, which may result in motor symptoms including spasticity.
New Drug Application (NDA)	The NDA is the process by which the U.S. FDA regulates and controls new drugs, and how a drug sponsor formally proposes that the FDA approve a new drug for sale and marketing in the U.S. Safety and efficacy data gathered in animal and human clinical trials of an IND are part of the NDA. The data must support product labeling that defines the appropriate patient population and information to enable safe and effective use.

TERM	DEFINITION
Pediatric Evaluation of Disability Inventory (PEDI)	The PEDI is an assessment tool for children that measures capability and performance of functional activities in 3 content areas: self-care, mobility, and social function. Scores range from 0-100, with higher scores indicating lesser disability.
Pediatric Functional Independence Measure (WeeFIM)	The WeeFIM is a validated pediatric outcomes tool that measures disability in children with developmental disorders. It measures how much assistance a child needs to perform activities of daily living. It can be used to track functional improvement and goal attainment.
Penn Spasm Frequency Scale (PSFS)	The PSFS is a self-report tool that assesses a patient's perception of spasm frequency. Spasticity is rated on a scale of 0 to 4; a score of 0 indicates no spasm, and a score of 4 indicates spasms occurring more than 10 times per hour. The scale was created to assess the effect of ITB on spasm frequency in patients with spasticity due to SCI.
Pharmacokinetics	The time course of drug absorption, distribution, metabolism, and excretion.
Pharmacodynamics	The relationship between drug concentration at the site of action and its resulting effects; includes receptor binding and sensitivity, postreceptor effects, and chemical interactions.
Physician Rating Scale (PRS)	A quantitative observational clinical scale that evaluates gait in children with CP.
Posterior spine fusion (PSF)	Surgical technique used to join two or more vertebrae.
Quality Adjusted Life Year (QALY)	A QALY is a generic measure of effectiveness that encompasses both quality and quantity of life (i.e., survival), providing a consistent and common measure that healthcare funders can use to inform funding decisions.
Rand Social Support Survey	The Rand Social Support Survey is a self-assessment that measures four social support subscales and overall functional social support.
Rankin Scale (RS)	The RS is a clinician assessment of global disability in activities of daily living for patients with a neurological disability.

TERM	DEFINITION
Rehabilitation Institute of Chicago Caregiver Questionnaire (RIC CareQ)	The RIC CareQ is a caregiver assessment of ease of caregiving and activities of daily living in patients with severe spasticity.
Short Form Survey (SF-36)	The SF-36 is a patient assessment of health in eight dimensions: physical functioning, role limitation because of physical health, social functioning, vitality or energy, bodily pain, mental health, role limitation because of emotional problems, and general health.
Sickness Impact Profile (SIP)	The SIP is a yes/no patient self-assessment that measures psychosocial and physical quality of life in 12 categories (sleep and rest, eating, work, home management, recreation and pastimes, social interaction, alertness behavior, emotional behavior, communication, ambulation, mobility, and body care and movement). A lower score indicates improvement. It is designed to objectively assess outcomes from health care services. There are 2 versions of the SIP; one with 136 items and one with 68 items.
Snow Hygiene Score	A measurement of ability to clean and self-catheterize first described by Snow et al (1990) within a case series of 9 MS patients receiving botulinum toxin for spasticity. This score was used by Rawicki (1999) to measure hygiene in 18 patients with cerebral origin spasticity receiving ITB therapy.
Social Desirability Scale (SDS)	The Marlowe-Crowne SDS measures social desirability; the projection of favorable images of oneself during social interaction.
Spasticity	Spasticity is an abnormal increase in muscle tone caused by injury of upper motor neuron pathways regulating muscles. Spasticity may be a result of multiple sclerosis, cerebral palsy, stroke, brain injury, or spinal cord injury.
Spinal Cord Injury (SCI)	Injury to the spinal cord resulting in a change of normal motor, sensory, or autonomic function. Motor symptoms may include spasticity.

TERM	DEFINITION
Stroke	When blood supply in the brain is interrupted, cell death occurs (ischemic, resulting from impeded blood flow; hemorrhagic, due to bleeding in the brain). Long-term motor symptoms may include spasticity.
Stroke-Specific Quality of Life Scale (SSQL)	The SSQL measures a patient's functional status after stroke. It contains 49 items in 12 domains, measured on a 5 point scale.
Traumatic Brain Injury (TBI)	Traumatic brain injury, a form of acquired brain injury (ABI), is damage to the brain caused by an external mechanical force, such as a motor vehicle accident, explosive blast injury, or penetrating injury.
Visual Analog Scale (VAS)	The VAS is a response scale that indicates severity of characteristics that are subjective or cannot be directly measured. It is commonly presented as a continuum of values from 0 to 10.
Willingness-To-Pay Threshold	Willingness-to-pay threshold is a threshold above which treatments are no longer considered cost-effective. An ICER is meaningful with respect to this threshold, which is approximately £20,000-£30,000 in the United Kingdom, €40,000 in Europe, and $50,000-$100,000 in the United States (Shiroiwa 2010) .The probability of payers not paying for a therapy increases significantly with increases in the ICER. *Shiroiwa T, Sung YK, Fukuda T et al. International survey on willingness-to-pay (WTP) for one additional QALY gained: What is the threshold of cost effectiveness? Health Econ. 2010;19(4):422-437.*

CLINICIAN RESOURCES

U.S. TECHNICAL SERVICES	(800) 707-0933 Technical Services provides 24/7 product and technical help and urgent support for clinicians.
U.S. REIMBURSEMENT SERVICES	(800) 292-2903 Reimbursement Services provides information about coding, coverage in your area, state rules and regulations (utilization review), prior authorization, and state fee schedules.
GLOBAL MEDICAL INFORMATION SERVICE	(763) 526-3300 rs.NeuroMedicalAffairs@medtronic.com The Medical Information Service provides medical and scientific information to educate and support informed patient care and clinical practice decisions.
U.S. NATIONAL ANSWERING SERVICE FOR CLINICIANS	(800) 633-8766 Contact a Sales Representative in your area.
U.S. ADVERSE EVENT REPORTING	(800) 328-0810 rs.NEUAdverseEventReporting@medtronic.com Report a product complaint or patient adverse event.
U.S. CUSTOMER SERVICE	(888) 638-7627 Place an order or initiate a product return.
ITB THERAPY ONLINE RESOURCE CENTER	http://professional.medtronic.com/itbrc/index.htm Access resources for centers that are starting or expanding the management of ITB Therapy.

PATIENT RESOURCES

U.S. PATIENT SERVICES	(800) 510-6735 A resource for patients and caregivers with questions about their implanted pump system or treatment.
PATIENT WEBSITE	www.baclofenpump.com Information and resources for patients who are exploring severe spasticity treatment options or have a baclofen pump.
PUMP PARTNER APP	http://www.baclofenpump.com/living/patient-support/pump-app/index.htm This app, available for smartphones and tablets, gives patients and clinicians quick access to therapy and safety information. Pump Partner can help patients manage their treatment and be prepared in case of emergency. Patients can store information such as device serial number and next refill appointment.

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Cost Analysis of ITB Therapy

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LIORESAL® INTRATHECAL
(baclofen injection)

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 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).

DESCRIPTION

LIORESAL INTRATHECAL (baclofen injection) is a muscle relaxant and antispastic. Its chemical name is 4-amino-3-(4-chlorophenyl) butanoic acid, and its structural formula is:

Baclofen is a white to off-white, odorless or practically odorless crystalline powder, with a molecular weight of 213.66. It is slightly soluble in water, very slightly soluble in methanol, and insoluble in chloroform.

LIORESAL INTRATHECAL is a sterile, pyrogen-free, isotonic solution free of antioxidants, preservatives or other potentially neurotoxic additives indicated only for intrathecal administration. The drug is stable in solution at 37° C and compatible with CSF. Each milliliter of LIORESAL INTRATHECAL contains baclofen U. S. P. 50 mcg, 500 mcg or 2000 mcg and sodium chloride 9 mg in Water for Injection; pH range is 5.0 - 7.0. Each ampule is intended for SINGLE USE ONLY. Discard any unused portion. **DO NOT AUTOCLAVE**.

CLINICAL PHARMACOLOGY

The precise mechanism of action of baclofen as a muscle relaxant and antispasticity agent is not fully understood. Baclofen inhibits both monosynaptic and polysynaptic reflexes at the spinal level, possibly by decreasing excitatory neurotransmitter release from primary afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Baclofen is a structural analog of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), and may exert its effects by stimulation of the $GABA_B$ receptor subtype.

LIORESAL INTRATHECAL when introduced directly into the intrathecal space permits effective CSF concentrations to be achieved with resultant plasma concentrations 100 times less than those occurring with oral administration.

In people, as well as in animals, baclofen has been shown to have general CNS depressant prop-erties as indicated by the production of sedation with tolerance, somnolence, ataxia, and respiratory and cardiovascular depression.

Pharmacodynamics of LIORESAL INTRATHECAL:
Intrathecal Bolus:

Adult Patients: The onset of action is generally one-half hour to one hour after an intrathecal bolus. Peak spasmolytic effect is seen at approximately four hours after dosing and effects may last four to eight hours. Onset, peak response, and duration of action may vary with individual patients depending on the dose and severity of symptoms.

Pediatric Patients: The onset, peak response and duration of action is similar to those seen in adult patients.

Continuous Infusion:

LIORESAL INTRATHECAL'S antispastic action is first seen at 6 to 8 hours after initiation of continuous infusion. Maximum activity is observed in 24 to 48 hours.
Continuous Infusion: No additional information is available for pediatric patients.

Pharmacokinetics of LIORESAL INTRATHECAL:

The pharmacokinetics of CSF clearance of LIORESAL INTRATHECAL calculated from intrathecal bolus or continuous infusion studies approximates CSF turnover, suggesting elimination is by bulk-flow removal of CSF.

Intrathecal Bolus: After a bolus lumbar injection of 50 or 100 mcg LIORESAL INTRATHECAL in seven patients, the average CSF elimination half-life was 1.51 hours over the first four hours and the average CSF clearance was approximately 30 mL/hour.

Continuous Infusion: The mean CSF clearance for LIORESAL INTRATHECAL (baclofen injection) was approximately 30 mL/hour in a study involving ten patients on continuous intrathecal infusion. Concurrent plasma concentrations of baclofen during intrathecal administration are expected to be low (0- 5 ng/mL).

Limited pharmacokinetic data suggest that a lumbar-cisternal concentration gradient of about 4:1 is established along the neuroaxis during baclofen infusion. This is based upon simultaneous CSF sampling via cisternal and lumbar tap in 5 patients receiving continuous baclofen infusion at the lumbar level at doses associated with therapeutic efficacy; the interpatient variability was great. The gradient was not altered by position.

Six pediatric patients (age 8-18 years) receiving continuous intrathecal baclofen infusion at doses of 77-400 mcg/day had plasma baclofen levels near or below 10 ng/mL.

INDICATIONS AND USAGE

LIORESAL INTRATHECAL (baclofen injection) is indicated for use in the management of severe spasticity. Patients should first respond to a screening dose of intrathecal baclofen prior to consideration for long term infusion via an implantable pump. For spasticity of spinal cord origin, chronic infusion of LIORESAL INTRATHECAL via an implantable pump should be reserved for patients unresponsive to oral baclofen therapy, or those who experience intolerable CNS side effects at effective doses. Patients with spasticity due to traumatic brain injury should wait at least one year after the injury before consideration of long term intrathecal baclofen therapy. LIORESAL INTRATHECAL is intended for use by the intrathecal route in single bolus test doses (via spinal catheter or lumbar puncture) and, for chronic use, only in implantable pumps approved by the FDA specifically for the administration of LIORESAL INTRATHECAL into the intrathecal space.

Spasticity of Spinal Cord Origin: Evidence supporting the efficacy of LIORESAL INTRATHECAL was obtained in randomized, controlled investigations that compared the effects of either a single intrathecal dose or a three day intrathecal infusion of LIORESAL INTRATHECAL to placebo in patients with severe spasticity and spasms due to either spinal cord trauma or multiple sclerosis. LIORESAL INTRATHECAL was superior to placebo on both principal outcome measures employed: change from baseline in the Ashworth rating of spasticity and the frequency of spasms.

Spasticity of Cerebral Origin: The efficacy of LIORESAL INTRATHECAL was investigated in three controlled clinical trials; two enrolled patients with cerebral palsy and one enrolled patients with spasticity due to previous brain injury. The first study, a randomized controlled cross-over trial of 51 patients with cerebral palsy, provided strong, statistically significant results; LIORESAL INTRATHECAL was superior to placebo in reducing spasticity as measured by the Ashworth Scale. A second cross-over study was conducted in 11 patients with spasticity arising from brain injury. Despite the small sample size, the study yielded a nearly significant test statistic (p= 0.066) and provided directionally favorable results. The last study, however, did not provide data that could be reliably analyzed.

LIORESAL INTRATHECAL therapy may be considered an alternative to destructive neurosurgical procedures. Prior to implantation of a device for chronic intrathecal infusion of LIORESAL INTRATHECAL, patients must show a response to LIORESAL INTRATHECAL in a screening trial (see Dosage and Administration).

CONTRAINDICATIONS

Hypersensitivity to baclofen. LIORESAL INTRATHECAL is not recommended for intravenous, intramuscular, subcutaneous or epidural administration.

WARNINGS

LIORESAL INTRATHECAL is for use in single bolus intrathecal injections (via a catheter placed in the lumbar intrathecal space or injection by lumbar puncture) and in implantable pumps approved by the FDA specifically for the intrathecal administration of baclofen. Because of the possibility of potentially life- threatening CNS depression, cardiovascular collapse, and/or respiratory failure, physicians must be adequately trained and educated in chronic intrathecal infusion therapy.

The pump system should not be implanted until the patient's response to bolus LIORESAL INTRATHECAL injection is adequately evaluated. Evaluation (consisting of a screening procedure: see Dosage and Administration) requires that LIORESAL INTRATHECAL be administered into the intrathecal space via a catheter or lumbar puncture. Because of the risks associated with the screening procedure and the adjustment of dosage following pump implantation, these phases must be conducted in a medically supervised and adequately equipped environment following the instructions outlined in the Dosage and Administration section.

Resuscitative equipment should be available.

Following surgical implantation of the pump, particularly during the initial phases of pump use, the patient should be monitored closely until it is certain that the patient's response to the infusion is acceptable and reasonably stable.

On each occasion that the dosing rate of the pump and/or the concentration of LIORESAL INTRATHECAL (baclofen injection) in the reservoir is adjusted, close medical monitoring is required until it is certain that the patient's response to the infusion is acceptable and reasonably stable.

It is mandatory that the patient, all patient caregivers, and the physicians responsible for the patient receive adequate information regarding the risks of this mode of treatment. All medical personnel and caregivers should be instructed in 1) the signs and symptoms of overdose, 2) procedures to be followed in the event of overdose and 3) proper home care of the pump and insertion site.

Overdose: Signs of overdose may appear suddenly or insidiously. Acute massive overdose may present as coma. Less sudden and/or less severe forms of overdose may present with signs of drowsiness, lightheadedness, dizziness, somnolence, respiratory depression, seizures, rostral progression of hypotonia and loss of consciousness progressing to coma. Should overdose appear likely, the patient should be taken immediately to a hospital for assessment and emptying of the pump reservoir. In cases reported to date, overdose has generally been related to pump malfunction, inadvertent subcutaneous injection, or dosing error. (See Drug Overdose Symptoms and Treatment.)

Extreme caution must be used when filling an FDA approved implantable pump. Such pumps should only be refilled through the reservoir refill septum. Inadvertent injection into the subcutaneous tissue can occur if the reservoir refill septum is not properly accessed. Some pumps are also equipped with a catheter access port that allows direct access to the intrathecal catheter. Direct injection into this catheter access port or inadvertent injection into the subcutaneous tissue may cause a life-threatening overdose.

Withdrawal: Abrupt withdrawal of intrathecal baclofen, regardless of the cause, has resulted in sequelae that included high fever, altered mental status, exaggerated rebound spasticity and muscle rigidity that in rare cases progressed to rhabdomyolysis, multiple organ-system failure, and death. In the first 9 years of post-marketing experience, 27 cases of withdrawal temporally related to the cessation of baclofen therapy were reported; six patients died. In most cases, symptoms of withdrawal appeared within hours to a few days following interruption of baclofen therapy. Common reasons for abrupt interruption of intrathecal baclofen therapy included malfunction of the catheter (especially disconnection), low volume in the pump reservoir, and end of pump battery life; human error may have played a causal or contributing role in some cases. Cases of intrathecal mass at the tip of the implanted catheter leading to withdrawal symptoms have also been reported, most of them involving pharmacy compounded analgesic admixtures (see PRECAUTIONS).

Prevention of abrupt discontinuation of intrathecal baclofen requires careful attention to 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.

All patients receiving intrathecal baclofen therapy are potentially at risk for withdrawal. Early symptoms of baclofen withdrawal may include return of baseline spasticity, pruritus, hypotension, and paresthesias. Priapism may develop or recur if treatment with intrathecal baclofen is interrupted. Some clinical characteristics of the advanced intrathecal baclofen withdrawal syndrome may resemble autonomic dysreflexia, infection (sepsis), malignant hyperthermia, neuroleptic-malignant syndrome, or other conditions associated with a hypermetabolic state or widespread rhabdomyolysis.

Rapid, accurate diagnosis and treatment in an emergency-room or intensive-care setting are important in order to prevent the potentially life-threatening central nervous system and systemic effects of intrathecal baclofen withdrawal. The suggested treatment for intrathecal baclofen withdrawal is the restoration of intrathecal baclofen at or near the same dosage as before therapy was interrupted. However, if restoration of intrathecal delivery is delayed, treatment with GABA-ergic agonist drugs such as oral or enteral baclofen, or oral, enteral, or intravenous benzodiazepines may prevent potentially fatal sequelae. Oral or enteral baclofen alone should not be relied upon to halt the progression of intrathecal baclofen withdrawal.

Seizures have been reported during overdose and with withdrawal from LIORESAL INTRATHECAL as well as in patients maintained on therapeutic doses of LIORESAL INTRATHECAL.

Fatalities:

Spasticity of Spinal Cord Origin: There were 16 deaths reported among the 576 U.S. patients treated with LIORESAL INTRATHECAL (baclofen injection) in pre- and post- marketing studies evaluated as of December 1992. Because these patients were treated under uncontrolled clinical settings, it is impossible to determine definitively what role, if any, LIORESAL INTRATHECAL played in their deaths.

As a group, the patients who died were relatively young (mean age was 47 with a range from 25 to 63), but the majority suffered from severe spasticity of many years duration, were nonambulatory, had various medical complications such as pneumonia, urinary tract infections, and decubiti, and/or had received multiple concomitant medications. A case-by-case review of the clinical course of the 16 patients who died failed to reveal any unique signs, symptoms, or laboratory results that would suggest that treatment with LIORESAL INTRATHECAL caused their deaths. Two patients, however, did suffer sudden and unexpected death within 2 weeks of pump implantation and one patient died unexpectedly after screening.

One patient, a 44 year-old male with MS, died in hospital on the second day following pump implantation. An autopsy demonstrated severe fibrosis of the coronary conduction system. A second patient, a 52 year-old woman with MS and a history of an inferior wall myocardial infarction, was found dead in bed 12 days after pump implantation, 2 hours after having had documented normal vital signs. An autopsy revealed pulmonary congestion and bilateral pleural effusions. It is impossible to determine whether LIORESAL INTRATHECAL contributed to these deaths. The third patient underwent three baclofen screening trials. His medical history included SCI, aspiration pneumonia, septic shock, disseminated intravascular coagulopathy, severe metabolic acidosis, hepatic toxicity, and status epilepticus. Twelve days after screening (he was not implanted), he again experienced status epilepticus with subsequent significant neurological deterioration. Based upon prior instruction, extraordinary resuscitative measures were not pursued and the patient died.

Spasticity of Cerebral Origin: There were three deaths occurring among the 211 patients treated with LIORESAL INTRATHECAL in pre- marketing studies as of March 1996. These deaths were not attributed to the therapy.

PRECAUTIONS

Children should be of sufficient body mass to accommodate the implantable pump for chronic infusion. Please consult pump manufacturer's manual for specific recommendations.

Safety and effectiveness in pediatric patients below the age of 4 have not been established.

Screening

Patients should be infection-free prior to the screening trial with LIORESAL INTRATHECAL (baclofen injection) because the presence of a systemic infection may interfere with an assessment of the patient's response to bolus LIORESAL INTRATHECAL.

Pump Implantation

Patients should be infection-free prior to pump implantation because the presence of infection may increase the risk of surgical complications. Moreover, a systemic infection may complicate dosing.

Pump Dose Adjustment and Titration

In most patients, it will be necessary to increase the dose gradually over time to maintain effectiveness; a sudden requirement for substantial dose escalation typically indicates a catheter complication (i.e., catheter kink or dislodgement).

Reservoir refilling must be performed by fully trained and qualified personnel following the directions provided by the pump manufacturer. Inadvertent injection into the subcutaneous tissue can occur if the reservoir refill septum is not properly accessed. Subcutaneous injection may result in symptoms of a systemic overdose or early depletion of the reservoir. Refill intervals should be carefully calculated to prevent depletion of the reservoir, as this would result in the return of severe spasticity and possibly symptoms of withdrawal.

Strict aseptic technique in filling is required to avoid bacterial contamination and serious infection. A period of observation appropriate to the clinical situation should follow each refill or manipulation of the drug reservoir.

Extreme caution must be used when filling an FDA approved implantable pump equipped with an injection port that allows direct access to the intrathecal catheter. Direct injection into the catheter through the catheter access port may cause a life-threatening overdose.

Additional considerations pertaining to dosage adjustment: It may be important to titrate the dose to maintain some degree of muscle tone and allow occasional spasms to: 1) help support circulatory function, 2) possibly prevent the formation of deep vein thrombosis, 3) optimize activities of daily living and ease of care.

Except in overdose related emergencies, the dose of LIORESAL INTRATHECAL should ordinarily be reduced slowly if the drug is discontinued for any reason.

An attempt should be made to discontinue concomitant oral antispasticity medication to avoid possible overdose or adverse drug interactions, either prior to screening or following implant and initiation of chronic LIORESAL INTRATHECAL infusion. Reduction and discontinuation of oral antispasmotics should be done slowly and with careful monitoring by the physician. Abrupt reduction or discontinuation of concomitant antispastics should be avoided.

Drowsiness: Drowsiness has been reported in patients on LIORESAL INTRATHECAL. Patients should be cautioned regarding the operation of automobiles or other dangerous machinery, and activities made hazardous by decreased alertness. Patients should also be cautioned that the central nervous system depressant effects of LIORESAL INTRATHECAL (baclofen injection) may be additive to those of alcohol and other CNS depressants.

Intrathecal mass: Cases of intrathecal mass at the tip of the implanted catheter have been reported, most of them involving pharmacy compounded analgesic admixtures. The most frequent symptoms associated with intrathecal mass are: 1) decreased therapeutic response (worsening spasticity, return of spasticity when previously well controlled, withdrawal symptoms, poor response to escalating doses, or frequent or large dosage increases), 2) pain, 3) neurological deficit/dysfunction. Clinicians should monitor patients on intraspinal therapy carefully for any new neurological signs or symptoms. In patients with new neurological signs or symptoms suggestive of an intrathecal mass, consider a neurosurgical consultation, since many of the symptoms of inflammatory mass are not unlike the symptoms experienced by patients with severe spasticity from their disease. In some cases, performance of an imaging procedure may be appropriate to confirm or rule-out the diagnosis of an intrathecal mass.

Precautions in special patient populations: Careful dose titration of LIORESAL INTRATHECAL is needed when spasticity is necessary to sustain upright posture and balance in locomotion or whenever spasticity is used to obtain optimal function and care.

Patients suffering from psychotic disorders, schizophrenia, or confusional states should be treated cautiously with LIORESAL INTRATHECAL and kept under careful surveillance, because exacerbations of these conditions have been observed with oral administration.

LIORESAL INTRATHECAL should be used with caution in patients with a history of autonomic dysreflexia. The presence of nociceptive stimuli or abrupt withdrawal of LIORESAL INTRATHECAL (baclofen injection) may cause an autonomic dysreflexic episode.

Because LIORESAL is primarily excreted unchanged by the kidneys, it should be given with caution in patients with impaired renal function and it may be necessary to reduce the dosage.

LABORATORY TESTS

No specific laboratory tests are deemed essential for the management of patients on LIORESAL INTRATHECAL.

DRUG INTERACTIONS

There is inadequate systematic experience with the use of LIORESAL INTRATHECAL in combination with other medications to predict specific drug-drug interactions. Interactions attributed to the combined use of LIORESAL INTRATHECAL and epidural morphine include hypotension and dyspnea.

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No increase in tumors was seen in rats receiving baclofen orally for two years. Adequate genotoxicity assays of baclofen have not been performed.

PREGNANCY

There are no adequate and well-controlled studies in pregnant women. In animal studies, baclofen had adverse effects on embryofetal development when administered orally to pregnant rats. LIORESAL INTRATHECAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Baclofen given orally increased the incidence of fetal structural abnormalities (omphaloceles) in rats. Reductions in food intake and body weight gain were observed in the dams. Fetal structural abnormalities were not observed in mice or rabbits.

NURSING MOTHERS

In mothers treated with oral LIORESAL (baclofen USP) in therapeutic doses, the active substance passes into the milk. It is not known whether detectable levels of drug are present in milk of nursing mothers receiving LIORESAL INTRATHECAL. As a general rule, nursing should be undertaken while a patient is receiving LIORESAL INTRATHECAL only if the potential benefit justifies the potential risks to the infant.

PEDIATRIC USE

Children should be of sufficient body mass to accommodate the implantable pump for chronic infusion. Please consult pump manufacturer's manual for specific recommendations.

Safety and effectiveness in pediatric patients below the age of 4 have not been established.

Considerations based on experience with oral LIORESAL (baclofen USP)

A dose-related increase in incidence of ovarian cysts was observed in female rats treated chronically with oral LIORESAL. Ovarian cysts have been found by palpation in about 4% of the multiple sclerosis patients who were treated with oral LIORESAL for up to one year. In most cases these cysts disappeared spontaneously while patients continued to receive the drug. Ovarian cysts are estimated to occur spontaneously in approximately 1% to 5% of the normal female population.

ADVERSE REACTIONS

Spasticity of Spinal Cord Origin – Clinical Studies:

Commonly Observed in Patients with Spasticity of Spinal Origin — In pre- and post- marketing clinical trials, the most commonly observed adverse events associated with use of LIORESAL INTRATHECAL (baclofen injection) which were not seen at an equivalent incidence among placebo- treated patients were: somnolence, dizziness, nausea, hypotension, headache, convulsions and hypotonia.

Associated with Discontinuation of Treatment — 8/474 patients with spasticity of spinal cord origin receiving long term infusion of LIORESAL INTRATHECAL in pre- and post- marketing clinical studies in the U. S. discontinued treatment due to adverse events. These include: pump pocket infections (3), meningitis (2), wound dehiscence (1), gynecological fibroids (1) and pump overpressurization (1) with unknown, if any, sequela. Eleven patients who developed coma secondary to overdose had their treatment temporarily suspended, but all were subsequently re-started and were not, therefore, considered to be true discontinuations.

Fatalities — See Warnings.

Incidence in Controlled Trials — Experience with LIORESAL INTRATHECAL (baclofen injection) obtained in parallel, placebo-controlled, randomized studies provides only a limited basis for estimating the incidence of adverse events because the studies were of very brief duration (up to three days of infusion) and involved only a total of 63 patients. The following events occurred among the 31 patients receiving LIORESAL INTRATHECAL (baclofen injection) in two randomized, placebo-controlled trials: hypotension (2), dizziness (2), headache (2), dyspnea (1). No adverse events were reported among the 32 patients receiving placebo in these studies.

Events Observed during the Pre- and Post-marketing Evaluation of LIORESAL INTRATHECAL — Adverse events associated with the use of LIORESAL INTRATHECAL reflect experience gained with 576 patients followed prospectively in the United States. They received LIORESAL INTRATHECAL for periods of one day (screening) (N = 576) to over eight years (maintenance) (N = 10). The usual screening bolus dose administered prior to pump implantation in these studies was typically 50 mcg. The maintenance dose ranged from 12 mcg to 2003 mcg per day. Because of the open, uncontrolled nature of the experience, a causal linkage between events observed and the administration of LIORESAL INTRATHECAL cannot be reliably assessed in many cases and many of the adverse events reported are known to occur in

association with the underlying conditions being treated. Nonetheless, many of the more commonly reported reactions— hypotonia, somnolence, dizziness, paresthesia, nausea/vomiting and headache— appear clearly drug-related.

Adverse experiences reported during all U.S. studies (both controlled and uncontrolled) are shown in the following table. Eight of 474 patients who received chronic infusion via implanted pumps had adverse experiences which led to a discontinuation of long term treatment in the pre- and post-marketing studies.

INCIDENCE OF MOST FREQUENT (≥1%) ADVERSE EVENTS IN PATIENTS WITH SPASTICITY OF SPINAL ORIGIN IN PROSPECTIVELY MONITORED CLINICAL TRIALS

	Percent of Patients Reporting Events		
	N = 576 Screening[a]	N = 474 Titration[b]	N = 430 Maintenance[c]
Adverse Event	**Percent**	**Percent**	**Percent**
Hypotonia	5.4	13.5	25.3
Somnolence	5.7	5.9	20.9
Dizziness	1.7	1.9	7.9
Paresthesia	2.4	2.1	6.7
Nausea and Vomiting	1.6	2.3	5.6
Headache	1.6	2.5	5.1
Constipation	0.2	1.5	5.1
Convulsion	0.5	1.3	4.7
Urinary Retention	0.7	1.7	1.9
Dry Mouth	0.2	0.4	3.3
Accidental Injury	0.0	0.2	3.5
Asthenia	0.7	1.3	1.4
Confusion	0.5	0.6	2.3
Death	0.2	0.4	3.0
Pain	0.0	0.6	3.0
Speech Disorder	0.0	0.2	3.5
Hypotension	1.0	0.2	1.9
Ambylopia	0.5	0.2	2.3
Diarrhea	0.0	0.8	2.3
Hypoventilation	0.2	0.8	2.1
Coma	0.0	1.5	0.9
Impotence	0.2	0.4	1.6
Peripheral Edema	0.0	0.0	2.3
Urinary Incontinence	0.0	0.8	1.4
Insomnia	0.0	0.4	1.6
Anxiety	0.2	0.4	0.9
Depression	0.0	0.0	1.6
Dyspnea	0.3	0.0	1.2
Fever	0.5	0.2	0.7
Pneumonia	0.2	0.2	1.2
Urinary Frequency	0.0	0.6	0.9
Urticaria	0.2	0.2	1.2
Anorexia	0.0	0.4	0.9
Diplopia	0.0	0.4	0.9
Dysautonomia	0.2	0.2	0.9
Hallucinations	0.3	0.4	0.5
Hypertension	0.2	0.6	0.5

[a] Following administration of test bolus
[b] Two month period following implant
[c] Beyond two months following implant
N = total number of patients entering each period
% = % of patients evaluated

In addition to the more common (1% or more) adverse events reported in the prospectively followed 576 domestic patients in pre- and post-marketing studies, experience from an additional 194 patients exposed to LIORESAL INTRATHECAL (baclofen injection) from foreign studies has been reported. The following adverse events, not described in the table, and arranged in decreasing order of frequency, and classified by body system, were reported:

Nervous System: Abnormal gait, thinking abnormal, tremor, amnesia, twitching, vasodilitation, cerebrovascular accident, nystagmus, personality disorder, psychotic depression, cerebral ischemia, emotional lability, euphoria, hypertonia, ileus, drug dependence, incoordination, paranoid reaction and ptosis.

Digestive System: Flatulence, dysphagia, dyspepsia and gastroenteritis.

Cardiovascular: Postural hypotension, bradycardia, palpitations, syncope, arrhythmia ventricular, deep thrombophlebitis, pallor and tachycardia.

Respiratory: Respiratory disorder, aspiration pneumonia, hyperventilation, pulmonary embolus and rhinitis.

Urogenital: Hematuria and kidney failure.

Skin and Appendages: Alopecia and sweating.

Metabolic and Nutritional Disorders: Weight loss, albuminuria, dehydration and hyperglycemia.

Special Senses: Abnormal vision, abnormality of accommodation, photophobia, taste loss and tinnitus.

Body as a Whole: Suicide, lack of drug effect, abdominal pain, hypothermia, neck rigidity, chest pain, chills, face edema, flu syndrome and overdose.

Hemic and Lymphatic System: Anemia.

Spasticity of Cerebral Origin – Clinical Studies:

Commonly Observed — In pre-marketing clinical trials, the most commonly observed adverse events associated with use of LIORESAL INTRATHECAL (baclofen injection) which were not seen at an equivalent incidence among placebo-treated patients included: agitation, constipation, somnolence, leukocytosis, chills, urinary retention and hypotonia.

Associated with Discontinuation of Treatment — Nine of 211 patients receiving LIORESAL INTRATHECAL in pre-marketing clinical studies in the U.S. discontinued long term infusion due to adverse events associated with intrathecal therapy.

The nine adverse events leading to discontinuation were: infection (3), CSF leaks (2), meningitis (2), drainage (1), and unmanageable trunk control (1).

Fatalities — Three deaths, none of which were attributed to LIORESAL INTRATHECAL, were reported in patients in clinical trials involving patients with spasticity of cerebral origin. See Warnings on other deaths reported in spinal spasticity patients.

Incidence in Controlled Trials — Experience with LIORESAL INTRATHECAL (baclofen injection) obtained in parallel, placebo-controlled, randomized studies provides only a limited basis for estimating the incidence of adverse events because the studies involved a total of 62 patients exposed to a single 50 mcg intrathecal bolus. The following events occurred among the 62 patients receiving LIORESAL INTRATHECAL in two randomized, placebo-controlled trials involving cerebral palsy and head injury patients, respectively: agitation, constipation, somnolence, leukocytosis, nausea, vomiting, nystagmus, chills, urinary retention, and hypotonia.

Events Observed during the Pre-marketing Evaluation of LIORESAL INTRATHECAL — Adverse events associated with the use of LIORESAL INTRATHECAL reflect experience gained with a total of 211 U. S. patients with spasticity of cerebral origin, of whom 112 were pediatric patients (under age 16 at enrollment). They received LIORESAL INTRATHECAL for periods of

one day (screening) (N= 211) to 84 months (maintenance) (N= 1). The usual screening bolus dose administered prior to pump implantation in these studies was 50-75 mcg. The maintenance dose ranged from 22 mcg to 1400 mcg per day. Doses used in this patient population for long term infusion are generally lower than those required for patients with spasticity of spinal cord origin.

Because of the open, uncontrolled nature of the experience, a causal linkage between events observed and the administration of LIORESAL INTRATHECAL cannot be reliably assessed in many cases. Nonetheless, many of the more commonly reported reactions— somnolence, dizziness, headache, nausea, hypotension, hypotonia and coma— appear clearly drug-related.

The most frequent (≥1%) adverse events reported during all clinical trials are shown in the following table. Nine patients discontinued long term treatment due to adverse events.

INCIDENCE OF MOST FREQUENT (≥1%) ADVERSE EVENTS IN PATIENTS WITH SPASTICITY OF CEREBRAL ORIGIN IN PROSPECTIVELY MONITORED CLINICAL TRIALS

	Percent of Patients Reporting Events		
	N = 211 Screening[a]	**N = 153** Titration[b]	**N = 150** Maintenance[c]
Adverse Event	**Percent**	**Percent**	**Percent**
Hypotonia	2.4	14.4	34.7
Somnolence	7.6	10.5	18.7
Headache	6.6	7.8	10.7
Nausea and Vomiting	6.6	10.5	4.0
Vomiting	6.2	8.5	4.0
Urinary Retention	0.9	6.5	8.0
Convulsion	0.9	3.3	10.0
Dizziness	2.4	2.6	8.0
Nausea	1.4	3.3	7.3
Hypoventilation	1.4	1.3	4.0
Hypertonia	0.0	0.7	6.0
Paresthesia	1.9	0.7	3.3
Hypotension	1.9	0.7	2.0
Increased Salivation	0.0	2.6	2.7
Back Pain	0.9	0.7	2.0
Constipation	0.5	1.3	2.0
Pain	0.0	0.0	4.0
Pruritus	0.0	0.0	4.0
Diarrhea	0.5	0.7	2.0
Peripheral Edema	0.0	0.0	3.3
Thinking Abnormal	0.5	1.3	0.7
Agitation	0.5	0.0	1.3
Asthenia	0.0	0.0	2.0
Chills	0.5	0.0	1.3
Coma	0.5	0.0	1.3
Dry Mouth	0.5	0.0	1.3
Pneumonia	0.0	0.0	2.0
Speech Disorder	0.5	0.7	0.7
Tremor	0.5	0.0	1.3
Urinary Incontinence	0.0	0.0	2.0
Urination Impaired	0.0	0.0	2.0

[a] Following administration of test bolus
[b] Two month period following implant
[c] Beyond two months following implant
N = total number of patients entering each period. 211 patients received drug; (1 of 212) received placebo only.

The more common (1% or more) adverse events reported in the prospectively followed 211 patients exposed to LIORESAL INTRATHECAL (baclofen injection) have been reported. In the total cohort, the following adverse events, not described in the table, and arranged in decreasing order of frequency, and classified by body system, were reported:

Nervous System: Akathisia, ataxia, confusion, depression, opisthotonos, amnesia, anxiety, hallucinations, hysteria, insomnia, nystagmus, personality disorder, reflexes decreased, and vasodilitation.
Digestive System: Dysphagia, fecal incontinence, gastrointestinal hemorrhage and tongue disorder.
Cardiovascular: Bradycardia.
Respiratory: Apnea, dyspnea and hyperventilation.
Urogenital: Abnormal ejaculation, kidney calculus, oliguria and vaginitis.
Skin and Appendages: Rash, sweating, alopecia, contact dermatitis and skin ulcer.
Special Senses: Abnormality of accommodation.
Body as a Whole: Death, fever, abdominal pain, carcinoma, malaise and hypothermia.
Hemic and Lymphatic System: Leukocytosis and petechial rash.

Postmarketing Experience:

The following adverse events have been reported during post-approval use of LIORESAL INTRATHECAL. Because these events are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

Musculoskeletal: The onset of scoliosis or worsening of a pre-existing scoliosis has been reported.
Urogenital: Sexual dysfunction in men and women, including decreased libido and orgasm dysfunction, have been reported. Erectile dysfunction in men has also been reported. Priapism has been reported following baclofen withdrawal.

OVERDOSAGE

Special attention must be given to recognizing the signs and symptoms of overdosage, especially during the initial screening and dose-titration phase of treatment, but also during re- introduction of LIORESAL INTRATHECAL after a period of interruption in therapy.

Symptoms of LIORESAL INTRATHECAL Overdose: Drowsiness, lightheadedness, dizziness, somnolence, respiratory depression, hypothermia, seizures, rostral progression of hypotonia and loss of consciousness progressing to coma of up to 72 hr. duration. In most cases reported, coma was reversible without sequelae after drug was discontinued. Symptoms of LIORESAL INTRATHECAL overdose were reported in a sensitive adult patient after receiving a 25 mcg intrathecal bolus.

Treatment Suggestions for Overdose:

There is no specific antidote for treating overdoses of LIORESAL INTRATHECAL (baclofen injection); however, the following steps should ordinarily be undertaken:

1) Residual LIORESAL INTRATHECAL solution should be removed from the pump as soon as possible.

2) Patients with respiratory depression should be intubated if necessary, until the drug is eliminated.

If lumbar puncture is not contraindicated, consideration should be given to withdrawing 30-40 mL of CSF to reduce CSF baclofen concentration.

DOSAGE AND ADMINISTRATION

Refer to the manufacturer's manual for the implantable pump approved for intrathecal infusion for specific instructions and precautions for programming the pump and/or refilling the reservoir. There are various pumps with varying reservoir volumes and there are various refill kits available. It is important to be familiar with all of these products in order to select the appropriate refill kit for the particular pump in use.

Screening Phase: Prior to pump implantation and initiation of chronic infusion of LIORESAL INTRATHECAL (baclofen injection), patients must demonstrate a positive clinical response to a LIORESAL INTRATHECAL bolus dose administered intrathecally in a screening trial. The screening trial employs LIORESAL INTRATHECAL at a concentration of 50 mcg/mL. A 1 mL ampule (50 mcg/mL) is available for use in the screening trial. The screening procedure is as follows. An initial bolus containing 50 micrograms in a volume of 1 milliliter is administered into the intrathecal space by barbotage over a period of not less than one minute. The patient is observed over the ensuing 4 to 8 hours. A positive response consists of a significant decrease in muscle tone and/or frequency and/or severity of spasms. If the initial response is less than desired, a second bolus injection may be administered 24 hours after the first. The second screening bolus dose consists of 75 micrograms in 1.5 milliliters. Again, the patient should be observed for an interval of 4 to 8 hours. If the response is still inadequate, a final bolus screening dose of 100 micrograms in 2 milliliters may be administered 24 hours later.

Pediatric Patients: The starting screening dose for pediatric patients is the same as in adult patients, i.e., 50 mcg. However, for very small patients, a screening dose of 25 mcg may be tried first. **Patients who do not respond to a 100 mcg intrathecal bolus should not be considered candidates for an implanted pump for chronic infusion.**

Postimplant Dose Titration Period: To determine the initial total daily dose of LIORESAL INTRATHECAL following implant, the screening dose that gave a positive effect should be doubled and administered over a 24-hour period, unless the efficacy of the bolus dose was maintained for more than 8 hours, in which case the starting daily dose should be the screening dose delivered over a 24-hour period. No dose increases should be given in the first 24 hours (i.e., until the steady state is achieved).

Adult Patients with Spasticity of Spinal Cord Origin: After the first 24 hours, for adult patients, the daily dosage should be increased slowly by 10-30% increments and only once every 24 hours, until the desired clinical effect is achieved.

Adult Patients with Spasticity of Cerebral Origin: After the first 24 hours, the daily dose should be increased slowly by 5-15% only once every 24 hours, until the desired clinical effect is achieved.

Pediatric Patients: After the first 24 hours, the daily dose should be increased slowly by 5-15% only once every 24 hours, until the desired clinical effect is achieved. If there is not a substantive clinical response to increases in the daily dose, check for proper pump function and catheter patency. Patients must be monitored closely in a fully equipped and staffed environment during the screening phase and dose-titration period immediately following implant. Resuscitative equipment should be immediately available for use in case of life-threatening or intolerable side effects.

Maintenance Therapy:

Spasticity of Spinal Cord Origin Patients: The clinical goal is to maintain muscle tone as close to normal as possible, and to minimize the frequency and severity of spasms to the extent possible, without inducing intolerable side effects. Very often, the maintenance dose needs to be adjusted during the first few months of therapy while patients adjust to changes in life style due to the alleviation of spasticity. During periodic refills of the pump, the daily dose may be increased by 10-40%, but no more than 40%, to maintain adequate symptom control. The daily dose may be reduced by 10-20% if patients experience side effects. Most patients require gradual increases in dose over time to maintain optimal response during chronic therapy. A sudden large requirement for dose escalation suggests a catheter complication (i.e., catheter kink or dislodgement).

Maintenance dosage for long term continuous infusion of LIORESAL INTRATHECAL (baclofen injection) has ranged from 12 mcg/day to 2003 mcg/ day, with most patients adequately maintained on 300 micrograms to 800 micrograms per day. There is limited experience with daily doses greater than 1000 mcg/day. Determination of the optimal LIORESAL INTRATHECAL dose requires individual titration. The lowest dose with an optimal response should be used.

Spasticity of Cerebral Origin Patients: The clinical goal is to maintain muscle tone as close to nor- mal as possible and to minimize the frequency and severity of spasms to the extent possible, without inducing intolerable side effects, or to titrate the dose to the desired degree of muscle tone for optimal functions. Very often the maintenance dose needs to be adjusted during the first few months of therapy while patients adjust to changes in life style due to the alleviation of spasticity. During periodic refills of the pump, the daily dose may be increased by 5-20%, but no more than 20%, to maintain adequate symptom control. The daily dose may be reduced by 10-20% if patients experience side effects. Many patients require gradual increases in dose over time to maintain optimal response during chronic therapy. A sudden large requirement for dose escalation suggests a catheter complication (i.e., catheter kink or dislodgement).

Maintenance dosage for long term continuous infusion of LIORESAL INTRATHECAL (baclofen injection) has ranged from 22 mcg/ day to 1400 mcg/ day, with most patients adequately maintained on 90 micrograms to 703 micrograms per day. In clinical trials, only 3 of 150 patients required daily doses greater than 1000 mcg/ day.

Pediatric Patients: Use same dosing recommendations for patients with spasticity of cerebral origin. Pediatric patients under 12 years seemed to require a lower daily dose in clinical trials. Average daily dose for patients under 12 years was 274 mcg/ day, with a range of 24 to 1199 mcg/ day. Dosage requirement for pediatric patients over 12 years does not seem to be different from that of adult patients. Determination of the optimal LIORESAL INTRATHECAL dose requires individual titration. The lowest dose with an optimal response should be used.

Potential need for dose adjustments in chronic use: During long term treatment, approximately 5% (28/627) of patients become refractory to increasing doses. There is not sufficient experience to make firm recommendations for tolerance treatment; however, this

"tolerance" has been treated on occasion, in hospital, by a "drug holiday" consisting of the gradual reduction of LIORESAL INTRATHECAL over a 2 to 4 week period and switching to alternative methods of spasticity management. After the "drug holiday," LIORESAL INTRATHECAL may be restarted at the initial continuous infusion dose.

Stability

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit.

Delivery Specifications

The specific concentration that should be used depends upon the total daily dose required as well as the delivery rate of the pump. LIORESAL INTRATHECAL may require dilution when used with certain implantable pumps. Please consult manufacturer's manual for specific recommendations.

Preparation Instruction:

Screening

Use the 1 mL screening ampule only (50 mcg/mL) for bolus injection into the subarachnoid space. For a 50 mcg bolus dose, use 1 mL of the screening ampule. Use 1.5 mL of 50 mcg/mL baclofen injection for a 75 mcg bolus dose. For the maximum screening dose of 100 mcg, use 2 mL of 50 mcg/mL baclofen injection (2 screening ampules).

Maintenance

For patients who require concentrations other than 500 mcg/mL or 2000 mcg/mL, LIORESAL INTRATHECAL **must be diluted.**

LIORESAL INTRATHECAL **must be diluted** with sterile preservative free Sodium Chloride for Injection, U.S.P.

Delivery Regimen:

LIORESAL INTRATHECAL is most often administered in a continuous infusion mode immediately following implant. For those patients implanted with programmable pumps who have achieved relatively satisfactory control on continuous infusion, further benefit may be attained using more complex schedules of LIORESAL INTRATHECAL delivery. For example, patients who have increased spasms at night may require a 20% increase in their hourly infusion rate. Changes in flow rate should be programmed to start two hours before the time of desired clinical effect.

HOW SUPPLIED

LIORESAL INTRATHECAL (baclofen injection) is packaged in single use ampules containing 0.05 mg/1 mL (50 mcg/mL), 10 mg/20 mL (500 mcg/mL), 10 mg/5 mL (2000 mcg/mL), or 40 mg/20 mL (2000 mcg/mL) supplied as follows:

Screening dose (Model 8563s): one ampule containing 0.05 mg/1 mL (50 mcg/mL) (NDC 58281-562-01).

LIORESAL INTRATHECAL (baclofen injection) Refill Kits. Each refill kit includes the indicated amount of LIORESAL INTRATHECAL, a drug preparation kit, a pump refill kit with accessories that are compatible with Medtronic SynchroMed® Infusion Systems, and associated instructions.

Model 8561: one ampule containing 10 mg/20 mL (500 mcg/mL) (NDC 58281-560-01).

Model 8562: two ampules, each contains 10 mg/5 mL (2000 mcg/mL) (NDC 58281-561-02).
Model 8564: one ampule containing 40 mg/20 mL (2000 mcg/mL) (NDC 58281-563-01).
Model 8565: two ampules, each contains 10 mg/20 mL (500 mcg/mL) (NDC 58281-560-02).
Model 8566: two ampules, each contains 40 mg/20 mL (2000 mcg/mL) (NDC 58281-563-02).

Storage:

Does not require refrigeration.
Do not store above 86° F (30° C).
Do not freeze.
Do not heat sterilize.

Manufactured by Novartis Pharma Stein AG, Stein, Switzerland, for Medtronic, Inc., Minneapolis, Minnesota 55432-5604 USA.

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SynchroMed® II Drug Infusion System Brief Statement:

Product technical manuals and the appropriate drug labeling must be reviewed prior to use for detailed disclosure.

Indications:

US: Chronic intraspinal (epidural and intrathecal) infusion of preservative-free morphine sulfate sterile solution in the treatment of chronic intractable pain, chronic intrathecal infusion of preservative-free ziconotide sterile solution for the management of severe chronic pain, and chronic intrathecal infusion of Lioresal® Intrathecal (baclofen injection) for the management of severe spasticity; chronic intravascular infusion of floxuridine (FUDR) or methotrexate for the treatment of primary or metastatic cancer. Outside of US: Chronic infusion of drugs or fluids tested as compatible and listed in the product labeling.

Contraindications:

Infection; implant depth greater than 2.5 cm below skin; insufficient body size; spinal anomalies; drugs with preservatives, drug contraindications, drug formulations with pH ≤3, use of catheter access port (CAP) kit for refills or of refill kit for catheter access, blood sampling through CAP in vascular applications, use of Personal Therapy Manager to administer opioid to opioid-naïve patients or to administer ziconotide.

Warnings:

Non-indicated formulations may contain neurotoxic preservatives, antimicrobials, or antioxidants, or may be incompatible with and damage the system. Failure to comply with all product instructions, including use of drugs or fluids not indicated for use with system, or of questionable sterility or quality, or use of non-Medtronic components or inappropriate kits, can result in improper use, technical errors, increased risks to patient, tissue damage, damage to the system requiring revision or replacement, and/or change in therapy, and may result in additional surgical procedures, a return of underlying symptoms, and/or a clinically significant or fatal drug under- or overdose. Refer to appropriate drug labeling for indications, contraindications, warnings, precautions, dosage and administration, screening procedures and underdose and overdose symptoms and methods of management. Physicians must be familiar with the drug stability information in the product technical manuals and must understand the dose relationship to drug concentration and pump flow rate before prescribing pump infusion. Implantation and ongoing system management must be performed by individuals trained in the operation and handling of the infusion system. An inflammatory mass that can result in serious neurological impairment, including paralysis, may occur at the tip of the implanted catheter. Clinicians should monitor patients on intraspinal therapy carefully for any new neurological signs or symptoms, change in underlying symptoms, or need for rapid dose escalation.

Inform patients of the signs and symptoms of drug under- or overdose, appropriate drug warnings and precautions regarding drug interactions, potential side effects, and signs and symptoms that require medical attention, including prodromal signs and symptoms of inflammatory mass. If it is suspected or known that all or part of the drug was injected into the pocket during the refill procedure, monitor the patient closely for signs and symptoms of overdose in an appropriate facility for a sufficient amount of time or until the symptoms have resolved. Failure to recognize signs and symptoms and seek appropriate medical intervention can result in serious injury or death. Instruct patients to notify their healthcare professionals of the implanted pump before medical tests/procedures, to return for refills at prescribed times, to carry their Medtronic device identification card, to avoid manipulating the pump through the skin, to consult with their clinician if the pump alarms and before traveling or engaging in activities that can stress the infusion system or involve pressure or temperature changes. Strong sources of electromagnetic interference (EMI), such as short wave (RF) diathermy and MRI, can negatively interact with the pump and cause heating of the implanted pump, system damage, or changes in pump operation or flow rate, that can result in patient injury from tissue heating, additional surgical procedures, a return of underlying symptoms, and/or a clinically significant or fatal drug underdose or overdose. Avoid using shortwave (RF) diathermy within 30 cm of the pump or catheter. Effects of other types of diathermy (microwave, ultrasonic, etc.) on the pump are unknown. Drug infusion is suspended during MRI; for patients who cannot safely tolerate suspension, use alternative drug delivery method during MRI. Patients receiving intrathecal baclofen therapy are at higher risk for adverse events, as baclofen withdrawal can lead to a life threatening condition if not treated promptly and effectively. Confirm pump status before and after MRI. Reference product labeling for information on sources of EMI, effects on patient and system, and steps to reduce risks from EMI.

Precautions:

Monitor patients after device or catheter replacement for signs of underdose/overdose. Infuse preservative-free (intraspinal) saline or, for vascular applications, infuse heparinized solutions therapy at minimum flow rate if therapy is discontinued for an extended period of time to avoid system damage. EMI may interfere with programmer telemetry during pump programming sessions. EMI from the SynchroMed programmer may interfere with other active implanted devices (e.g., pacemaker, defibrillator, neurostimulator).

Adverse Events:

Include, but are not limited to, spinal/vascular procedure risks; infection; bleeding; tissue damage, damage to the system or loss of, or change in, therapy that may result in additional surgical procedures, a return of underlying symptoms, and/or a clinically significant or fatal drug underdose or overdose, due to end of device service life, failure of the catheter, pump or other system component, pump inversion, technical/programming errors, injection into the pocket or subcutaneous tissue or improper use, including use of non-indicated formulations and/or not using drugs or system in accordance with labeling; pocket seroma, hematoma, erosion, infection; post-lumbar puncture (spinal headache); CSF leak and rare central nervous system pressure-related problems; hygroma; radiculitis; arachnoiditis; spinal cord bleeding/damage; meningitis; neurological impairment (including paralysis) due to inflammatory mass; potential serious adverse effects from catheter fragments in intrathecal space, including potential to compromise antibiotic effectiveness for CSF infection; anesthesia complications; body rejection phenomena; local and systemic drug toxicity and related side effects; potential serious adverse effects from catheter placement in intravascular applications.

Lioresal® is a registered trademark of Saol.

USA Rx Only

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