

Evidence of the effects of intrathecal baclofen for spastic and dystonic cerebral palsy

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The objective of this and other systematic reviews by the American Academy for Cerebral Palsy and Developmental Medicine (AAPDM) is to provide the biomedical research and clinical practice communities with current knowledge about evidence supporting various interventions used in the management of developmental disabilities. "Systematic, evidence-based reviews are innovative in their comprehensive review of the literature, use of standard methods of presenting data, and special emphasis on the validity of research methods." (p.470)¹ AAPDM reviews summarize what is known and not yet known, to identify the gaps in our information about treatment outcomes and to gauge the strength of the internal validity of that evidence^a.

AACPDM reviews are not to be construed as practice guidelines, nor do they indicate the extent to which available evidence may be applicable to other people. Until comprehensive and robust bodies of evidence, necessary to determine generalizability of research findings, do become available, clinicians must rely on 'best evidence' to guide their treatment recommendations^b. Clinical relevance of the

outcomes, including benefits or risk judgments, must also be determined by the individual clinician from the data, often limited, in the evidence tables. Unfortunately, whether a difference between groups is clinically important is frequently difficult to ascertain, as there is no clear and standard criteria for deciding or because authors do not address the issue.

Method

INCLUSION CRITERIA

Intrathecal baclofen (ITB) therapy is variously referred to as intrathecal baclofen, intrathecally-administered baclofen, intrathecal baclofen infusion; and continuous intrathecal baclofen infusion. This review includes only studies of ITB administered into the lumbar spinal fluid either by (1) bolus injections, (2) an external pump that delivers a continuous infusion of baclofen, or (3) a surgically implanted pump that delivers a continuous infusion.

Part 1 includes all studies in which (1) participants were diagnosed with spastic type cerebral palsy (CP) or primarily spasticity mixed with other types of abnormal movement or

(2) in which specific data about any size subgroup of such individuals were provided.

Part 2 includes studies of participants with dystonic type CP.

LITERATURE SEARCH

The literature was searched through the MEDLINE database (from 1956 to March 2000) using two search programs (Clinical Query of PubMed and EndNote) and the exploded terms intrathecal baclofen, cerebral palsy, spasticity, dystonia, or athetosis as well as types of studies (e.g. clinical trials). Reference lists in studies, review articles, and researchers knowledgeable about this intervention were also consulted.

Organization of evidence

AACDPM guidelines for classifying the outcomes were followed^{2,3}. Each result was classified according to the dimension of disablement affected (Table 1)² and by the level of evidence it represents (Table 2)². Dimensions of disablement is a classification that facilitates the measurement, management, and research of rehabilitation outcomes and minimizes the barriers between medical and social models of rehabilitation. Levels of evidence and other quality-rating schemes start with a hierarchy of research designs that range from the greatest to least ability to reduce bias and conclude with assessment of the soundness with which the research was carried out. Generally speaking, Level I studies produce the strongest and most definitive evidence⁴. Level II studies produce tentative conclusions. Levels III and IV merely suggest causation. No conclusions regarding treatment efficacy can be drawn from Level V evidence.

Part 1. Effects of ITB in spastic CP

Spasticity is a common problem in many conditions that affect motor function, among them stroke, head injury, spinal cord injury, multiple sclerosis, various dystrophies, and CP. An underlying assumption in the treatment of spasticity is that spasticity may impede or mask existing motor control. The relation between spasticity and motor function, however, has been an issue of debate for many years. Some authors have argued that reduction of spasticity may impair, rather than improve, motor function if individuals rely upon their stiffness or hypertonicity for support during standing or walking^{5,6}. Additional goals of ITB treatment are to retard or prevent contractures, improve positioning and comfort, and, for individuals with severe spasticity, ease the tasks of their caregivers.

Baclofen's mechanism of action is based on the premise

that spasticity is associated with the inadequate release of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA)^{7,8}. Baclofen's molecular structure resembles that of GABA (with the exception of a substitution in the aliphatic chain) and appears to stimulate GABA b receptors⁷. Oral baclofen has been used for spasticity in CP since 1977. In the 1980s, lumbar intrathecal administration of baclofen was pioneered by Penn and Kroin in individuals with spasticity of spinal origin, specifically, multiple sclerosis and traumatic spinal cord injuries. Oral baclofen results in virtually undetectable levels of the drug in the spinal cord, whereas intrathecally administered baclofen at 1/100th the dose results in cerebrospinal fluid levels comparable to serum levels following oral medication.⁹⁻¹¹

Summary of studies

Seventeen relevant publications were identified for our study; three did not meet the inclusion criteria because each included only a few study participants with CP for which no specific results were reported.²⁶⁻²⁸ Twelve of the studies report treatment outcomes, one reports only adverse effects or complications¹⁷, and one is a cost analysis only¹⁶.

Table III summarizes the 14 studies on which the evidence tables are based. It contains information about the interventions, study participants, and research methodologies. In each study, the treatment was either bolus injections of ITB or continuous intrathecal administration via an external pump or a surgically implanted (internal) pump. 'Control' conditions within single individuals included observation of outcomes during placebo administration or no-treatment phases with outcomes during treatment-with-ITB phases. Although before-and-after studies (case studies and case series) compare outcomes before ITB with outcomes after being treated with ITB, technically, this does not constitute a 'control' because the treatment is not being 'experimentally manipulated' by the investigator.

Participant characteristics (with the exception of sex) are shown to the extent to which they were provided in the publications. Ten studies consisted of various investigations in three pools of participants. Five of these studies report on a

^a The concept of a 'quality grade' for articles used in systematic reviews is a matter of some debate, and the science of critical appraisal of the strength or validity of research is still evolving. Indeed, the science of critical appraisal of research is based on diseases in adults and the extent to which it is applicable to research about disabling conditions in developing children is also controversial. There is agreement, however, that teams developing authoritative, systematic reviews can take certain steps to ensure that their approaches to grading the quality of research results meet current scientific standards.

^b 'Best evidence' is represented by the study (or studies) that most closely approximates the patient characteristics of interest to the clinician, that used a therapeutic regime most like the one the clinician can provide, that investigated outcomes of greatest concern to this patient, and that provides the most credible or internally valid results.

Table I: Dimensions of disablement

<i>Dimension</i>	<i>Description</i>
Pathophysiology	Interruption or interference of normal physiology and developmental processes or structures
Impairment	Loss or abnormality of body structure or body function
Functional limitation/Activity	Restriction of ability to perform activities
Disability/Participation	Restricted participation in typical societal roles
Societal limitation/Context factors	Barriers to full participation imposed by societal attitudes, architectural barriers, social policies, and other external factors

total of 137 participants from the Children's Hospital of Pittsburgh, PA, but these were not 137 separate individuals^{12-14, 22, 23}. The extent of the probable overlap of the participants in these studies cannot be determined from the published reports or direct contact with the researchers. (Personal communication, MB). Three of the studies reported on 51 participants in a U S Federal Drug Administration-approved multi-center study^{17, 21, 24}, and two studies on a group of 19 children at British Columbia's Children's Hospital, Canada.

Information about the methodology includes a quality rating of each study (i.e. level of evidence). Level of evidence is influenced by the fact that much of the data about cerebral palsy have had to be teased out in many of the studies. The data about ITB for CP comes, in part, from studies that were the first investigations of ITB for spasticity of any cerebral origin, thus some studies included diagnoses other than CP. Where studies of participants with mixed diagnoses did provide separate results, only those results for the participants with CP are shown in the subsequent evidence tables. Three studies did not give specific CP results; however, both were predominantly composed of subjects with CP (approximately 90% in each)^{13, 22}. One cannot know the extent to which the group outcomes were affected by the medical conditions of the participants who had diagnoses other than CP. Four studies employed two different research designs, yielding different levels of evidence for the treatment outcomes, in each case single subject randomized controlled trials (i.e. N-of-1 RCTs) produced the shorter-term outcomes and less rigorous single-subject designs produced the longer-term outcomes^{17, 19, 20, 25}. Two others were case series, each sub-divided to create two smaller series (severely versus moderately involved participants), for which separate data were reported^{13, 21}.

Summary of results

The studies reported their results in one of two ways. One type of result compared outcomes during treatment with ITB versus those outcomes measured in the absence of ITB, including placebo. If the average score of the group improved during intrathecal administration of baclofen on a particular measure and that average score was statistically significant,

the result favored the ITB treatment. If the average score for the group was better during placebo or in the absence of ITB, the result represented a worsening of the outcome of interest. If the average of the group score was unchanged before and after ITB or the score of a group receiving ITB was no different from a group not receiving ITB, or the difference was not statistically significant, the result did not support ITB treatment.

The other type of result encountered was the variation of an outcome within a group of treated individuals. In other words, this type of result differentiated how many individuals in a single group treated with ITB improved, how many got worse, and/or how many were unchanged.

Readers interested in the measures used and clinical and statistical significance of each result can find this information in an additional summary of results table in the online version of this article at www.aacpdm.org. That table displays each of the outcomes that were investigated in the studies, the dimension of disability which would be affected, the measure that was used to evaluate the outcome, the result of that measure, inferential statistical data, and the level of evidence each result represents. All anecdotal outcomes were coded as Level V evidence, regardless of the level of evidence assigned to the study which produced them; this is because bias is not controllable in anecdotal reports.

Evidence tables

The evidence table (Table IV) appears in two sections to include the two types of results. Each result is represented in the table by its level of evidence (III to VII) and/or a superscripted number citing the study that produced that result.

SECTION 8. OUTCOMES WHEN TREATMENT WAS COMPARED WITH NO TREATMENT OR PLACEBO

Section 1 aggregates the 72 results of ITB treatment when compared to placebo or no treatment (including before and after treatment measurements). Scanning the columns allows visual assessment of outcomes that improved during ITB, versus outcomes that worsened, or that were either unchanged or lacked statistical significance. Scanning the rows, one can see how many times an outcome has been

Table II: Levels of evidence

<i>Level</i>	<i>Non-empirical</i>	<i>Group research</i>	<i>Outcomes research</i>	<i>Single subject research</i>
I		Randomized controlled trial All or none case series		N-of-1 randomized controlled trial
II		Nonrandomized controlled trial Prospective cohort study with concurrent control group	Analytic survey	ABABA design Alternating treatments Multiple baseline across subjects
III		Case-control study Cohort study with historical control group		ABA design
IV		Case series and registries without control group		AB design
V	Case report Anecdote Expert opinion Theory based on physiology, bench, animal research Common sense/first principles			

measured and consistency of results found across studies. Focusing on the roman numerals allows assessment of the range of the levels of evidence as well as the general strength of the individual outcomes and the overall body of evidence. More in-depth interpretation can be achieved by using the citations to track back to the summary tables to discern, for

example, the measure used to assess that outcome, the duration of treatment that produced it, the age of the study's participants, and so on. For readers who want to examine the study directly to learn more about the reliability and validity of the evaluation tools, and so on, the superscripted number also identifies the journal article in the reference section.

Table III: Summary of studies (spasticity): intervention, participants, and research methods
Section 1. Intervention and participants

Study	Treatment	Control	Participant characteristics	Nr of Participants		Age(y)
				Total	With CP	
Albright 1991 ¹²	Daily 25, 50, or 100µg bolus injection	Placebo	Moderately severe spastic quadriplegic CP (spasticity probably used in standing)	23 [ⓐ]	17	5–27
Albright 1993 ¹³	Internal pump [ⓑ]		Moderate-severe LE + UE spasticity of cerebral origin (spastic CP, TBI, post-encephalitis)	37	33	5–27
			Functional group [ⓐ]		25	
			Non-functional group [ⓐ]		8	
Albright 1995 ¹⁴	Internal pump	[ⓐ]	Moderately spastic CP (spasticity used in standing) and severe spastic quadriplegic CP	38	38	?
Penn 1995 ¹⁵	50-100 µg bolus injection		Spasticity in various motor disorders (rigidity, dystonia, TBI, quadriplegia CP with athetosis)	18	2	13, 42
Steinbok 1995 ¹⁶	Internal pump		Severe spastic quadriplegic CP	9	9	?
Gilmartin 1995 ¹⁷	Internal pump (except only bolus in 8)		Spastic CP	51	51	3–31
			No seizure history		32	
			Using antiepileptic drugs		19	
Latash 1996 ¹⁸	Bolus injection/day	Placebo	Spasticity of different etiology (SCI, MS, TBI, spinal stenosis, dystonia, stiff man syndrome, CP)	12	2	11, 11
Almeida 1997 ¹⁹	Phase 1. Bolus injection/day	Phase 1. Placebo	Spastic diplegic CP (ambulatory with manual wheelchair community mobility)	1	1	11
	Phase 2. Internal pump	Phase 2. No ITB		1	1	
Armstrong 1997 ²⁰	Phase 1: Bolus injection/day	Phase 1. Placebo	Severe spasticity of whole body that interferes with daily care from stable condition of cerebral origin (TBI, Leigh syndrome, CP)	19	10	4–19
	Phase 2. Internal pump					
Krach 1997 ²¹	Internal pump		Spastic CP/LE Ashworth score ≥ 3	44	44	4–31
			Less severe group [ⓐ]			
			More severe group [ⓐ]			
Gerszten 1997 ²²	Internal pump		Spasticity of cerebral origin (21, CP; 3, TBI); ambulatory ± assistive devices	24	21	9–30
Gerszten 1998 ²³	Internal pump		Spastic quadriplegic (40 cases) and diplegic (8 cases) CP	48	28 [ⓐ]	5–43
Gilmartin 2000 ²⁴	Phase 1: 50 µg bolus injection [ⓐ]	Phase 1: Placebo	Spastic CP (congenital or acquired before age 2); 35 quadriplegia, 4 diplegia, 4 paraplegia; moderate-severe	51	51	4–31
	Phase 2: CIBI			44	44	
Van Schaeuybroeck 2000 ²⁵	Phase 1: 25, 50, 75, 100 µg bolus injection	Phase 1: Placebo	Spasticity of cerebral origin (9 CP, 1 CCI, 1 subarachnoid hemorrhage): 9 severe, 3 moderate; 8 quadriplegia, 2 hemiplegia, 1 diplegia; 9 moderate-severe MR, 2 normal IQ; 4 seizure history	11	9	8–55
	Phase 2: Internal pump			6 [ⓐ]	≥ 4	

[ⓐ] Enrollment was also offered to a 2nd group of six participants with spasticity associated with other cerebral damage (TBI, mucopolysaccharidosis, athetoid CP); data for this subgroup not included here.

[ⓑ] Surgically implanted pump for continuous intrathecal baclofen infusion into lumbar spinal fluid.

[ⓐ] Ambulatory with and without aids.

[ⓐ] Non-ambulatory and dependent in all activities.

[ⓐ] Although this study compared outcomes of two case series (one treated with ITB, the other selective posterior rhizotomy); data (before and after) for ITB series only is included here.

[ⓐ] Investigators reviewed 48 cases but only 28 were relevant to data included here.

[ⓐ] Participants without positive response went on to open trial (no placebo) of single bolus of 75 µg and 100µg; positive response to one of these dosages required to participate in Phase 2.

[ⓐ] Phase 2 the number of participants to be eight but results were given for only six participants.

SECTION 2. OUTCOMES REPORTED AS UNIFORMITY OF RESULTS WITHIN TREATED GROUPS.

Section 2 of this table aggregates the 44 results that describe knowledge of the variation of ITB effect within treated groups.

How to read and interpret the evidence table

What evidence is there, for example, about the effect of ITB on muscle tone? Section 1 shows that muscle tone (general, upper extremity, lower extremity, or at hips, knees, and ankles) has been measured 25 times in seven studies, comparing tone during ITB to tone in the absence of ITB^{12–15, 19, 24, 25}. With the exception of one result about tone at the ankle, the results for reduction of muscle tone, in general or in the lower extremities, was consistent and positive. The 17 results that were evaluated were statistically significant. The results about upper-extremity tone were less consistent: five showed statistically significant improvement while five showed either no change or lacked statistical significance. Note that two of the unchanged and/or not statistically significant (*ns*) results came from the same study¹⁹ which contained only one participant (see Table III, summary of studies). The summary of results table at www.aacpdm.org will show that one of these two results represents a short-term outcome, the other, long-term.

Section 2 of the evidence table gives additional data about muscle tone based on the type of result that demonstrates variation of response to the intervention: 13 of 17 participants in one study¹² and six of 10 in another²⁰ had improved muscle tone with ITB, but some participants in both studies had unchanged muscle tone. The citation allows one to see that these results were from bolus screening trials

by referring back to the summary of studies, Table III.

Readers who want to target the data more specifically to aid in decision-making about a particular type of patient can identify results available from study participants similar to the patient. For example, if one is considering ITB for an ambulatory patient, Table III indicates that only three studies contain data that may be appropriate, i.e. from a 'functional' subgroup of 25 participants¹³, an ambulatory single participant with spastic diplegia¹⁹, and a 'less severe' subgroup of an unknown number²¹.

Caution is advised concerning the correct interpretation of results that were not statistically significant. Results may be *ns* because of lack of adequate power in the study. The power of a study is the probability that the study, given its design and sample size, can detect a true difference of a predetermined magnitude (effect size). In the absence of a power calculation in a study description, there is always the possibility that a true difference existed between the two conditions being compared, but that there was inadequate power to detect the difference. However, if a power calculation is reported and the sample size needed to produce the power is obtained, then a *ns* result statistically supports the conclusion that there is no difference between the two conditions compared. None of these ITB studies reported power calculations; thus their power is unknown and their *ns* results are more appropriately regarded as inconclusive than negative.

Adverse effects and medical complications

With the exception of one study²⁴, adverse effects and medical complications were not specifically available for the participants with CP. Complications were reported for all

Table III: Continued

Section 2. Research methodology

<i>Study</i>	<i>Research design</i>	<i>LOE</i>	<i>Duration of Rx</i>	<i>Rx group (n)</i>	<i>Control group (n)</i>	<i>CP results</i> [Ⓢ]
Albright ¹²	Multiple crossover trial*	I	8 h	17	17 [Ⓢ]	yes
Albright ¹³	Prospective case series					
	Functional group	IV	24 mo	25		yes
	Non-functional group	IV	12 mo	12		no
Albright ¹⁴	Retrospective case series	V	12 mo	38		yes
Penn ¹⁵	Case reports from case series	V	?	2		yes
Steinbok ¹⁶	Case series cost analysis	IV	12 mo	9		yes
Gilmartin ¹⁷	Retrospective case series	V	0–24 mo	51		yes
Latash ¹⁸	Case reports from double blind controlled trials	V	2 d	2		yes
Almeida ¹⁹	Phase 1. N-of-1 RCT	II	2 mo	1	1 [Ⓢ]	yes
	Phase 2. ABABAB design	III	2 y	1	1 [Ⓢ]	yes
Armstrong ²⁰	Phase 1. N-of-1 controlled trial	III	2 wk	10	10 [Ⓢ]	yes
	Phase 2. AB single subject design	V	12 mo	6	?	yes
Krach ²¹	Prospective case series	IV	12 mo	44		yes
Gerszten ²²	Retrospective case series	V	12–93 mo	24		no
Gerszten ²³	Retrospective case series	V	24–94 mo	28		yes
Gilmartin ²⁴	Phase 1: Multiple crossover trial	I	3 d	51	51 [Ⓢ]	yes
	Phase 2: AB single subject design	V	4–48 mo	44		yes
Van Schaeboeck ²⁵	Phase 1: Multiple crossover trial*	II	?d	6	9 [Ⓢ]	no
	Phase 2: ABA single subject design	III	12 mo	6	6 [Ⓢ]	no

LOE, level of evidence; Rx, treatment or intervention.

* Replicated N-of-1 randomized controlled trials (RCT) summed for group comparison with inferential statistics.

Ⓢ Participants were their own controls.

Ⓢ Data exclusively from participants with spastic CP is reported.

RCT, Randomized controlled trial.

participants with spasticity of cerebral origin in the other five studies that reported complications^{12, 13, 20, 22–25}.

Analysis and discussion of the evidence

1. WHAT EVIDENCE EXISTS ABOUT THE EFFECTS OF ITB ON SPASTICITY AND OTHER IMPAIRMENTS OF MOTOR FUNCTION IN INDIVIDUALS WITH CP AND HOW UNIFORM ARE THOSE EFFECTS?^c

Signs of spasticity

Although muscle tone measures have primarily been used to assess spasticity, other signs of spasticity (clonus, spasms,

and reflexes) were also measured in these studies. Of 32 measures of spastic signs (see Table IV, section 1), 26 showed reduction of spasticity. Effect on upper-extremity tone was inconclusive because the findings were inconsistent: five results indicated improvement and five indicated no change. It should be noted, however, that upper-extremity tone was initially near normal in some of the participants whose upper-extremity tone was unchanged or not statistically significant, so there may have been minimal potential for change^d. Long-term data from the multicenter study showed a trend toward increasing improvement over time (3 to 48

Table IV: Evidence table: state of knowledge about outcomes of treatment with ITB for spasticity in CP.

Section 1. Results of treatment compared with no treatment or placebo. The evidence about each outcome is indicated by its level of evidence code (I through V). The superscripted number references the study which produced the result. For example, positive and statistically significant results have been found for lower-extremity muscle tone three times (two Level II findings and one Level IV) in two different studies. Positive results without statistical validity have been found twice in the same study; one a Level II finding from the short-term part of the study and the other a Level III finding from the long-term, discernible by studying a summary of results table available at www.aacpdm.org

<i>Outcomes by dimensions of disability</i>	<i>Improvement with ITB</i>		<i>Deterioration with ITB</i>		<i>Unchanged and/or not statistically significant results</i>
	<i>Statistically significant (p ≤ 0.05)</i>	<i>Not statistically evaluated</i>	<i>Statistically significant (p ≤ 0.05)</i>	<i>Not statistically evaluated</i>	
Pathophysiology					
Impairment					
Muscle tone: general	II ^{25,25,25} V ¹⁵				
Muscle tone: lower extremity	I ^{12,24,21} IV ^{13,13}	II ¹⁹ III ¹⁹			
Muscle tone: upper extremity	I ^{24,21} II ²⁵ IV ¹³ V ¹⁴				I ¹² II ^{19,25} III ¹⁹ IV ¹²
Muscle tone: hip	II ²⁵				
Muscle tone: knee	II ²⁵				II ²⁵
Muscle tone: ankle					
Clonus		II ¹⁹			
	III ¹⁹ V ¹⁸				
Spasms					
Babinski reflex		II ¹⁹ III ¹⁹			
Range of motion: lower extremity		II ¹⁹		III ¹⁹	
Range of motion: knee	IV ¹³				IV ¹³
Range of motion: ankle					IV ^{13,13}
Range of motion: hip					IV ^{13,13}
Range of motion: upper extremity					V ¹⁴
Strength: lower extremity				II ¹⁹ III ¹⁹	
Strength: upper extremity			V ¹⁸	II ¹⁹ III ¹⁹	
Movement quality: lower extremity		II ¹⁹			
Movement quality: upper extremity		II ¹⁹			V ¹⁸
Functional limitation/activity					
Upper-extremity function	IV ¹³				I ¹²
Activities of daily living	IV ¹³				II ²⁵ IV ^{13,13}
Dressing		V ^{19,19}			
Eating		V ^{19,19}			
Toileting		V ¹⁹			
Transferring		V ¹⁹			IV ¹³
Gross motor activities		III ¹⁹			II ¹⁹
Lying/rolling	IV ^{21,21}				
Sitting	IV ²¹				IV ²¹
Crawling	IV ²¹				IV ^{21,21}
Disability/participation					
School fitness program		V ¹⁹			
Societal limitation/context					
Cost (\$)				IV ¹⁶	

^c No mechanism of action in athetosis has been suggested, but informal observations were made about effects of ITB on the athetoid movement in nine participants who had mixed spasticity and athetosis. 13,15 No effect on athetosis was noted.

months) with ITB in both upper and lower extremities, but greater improvement in the lower.²⁴ Higher concentrations of ITB or inserting the catheter at a higher level have been suggested to improve effect in the upper extremities²⁵.

While the group mean data (Table III, section 1) suggested that ITB suppressed spasticity in the lower extremities (or unspecified muscles), it was not detected for all participants. Data in section 2 of the table shows that clinically important suppression did not occur in four of 17 participants in one study and four of 10 participants in another^{12,20}. Upper extremity tone was suppressed in three of six²⁰. Five of six participants experienced suppression of spasms²⁵.

Table IV: Continued

Section 2. Evidence about uniformity of results within treated groups. The number of participants within a treated group (e.g. 13/17) is followed by a level of evidence indicating the credibility of the result and the citation for the study that produced the result. For example, a study that investigated gait²² reported how many improved, how many worsened, and how many were unchanged as a result of ITB treatment, whereas a study that investigated alertness²¹ reported only the number who improved. Sometimes two or more results from different measures of the same outcome are provided by the same study.

<i>Outcomes by dimensions of disability</i>	<i>Positive results</i>	<i>Negative results</i>	<i>Unchanged results</i>
Pathophysiology			
Impairment			
Muscle tone: unspecified	13/17 I ¹² 6/10 V ²⁰		4/17 I ¹² 4/10 V ²⁰
Muscle tone: lower extremity	4/6 V ²⁰		2/6 V ²⁰
Muscle tone: upper extremity	3/6 V ²⁰		3/6 V ²⁰
Spasms	5/6 IV ²⁵		1/6 IV ²⁵
Strength		1/25 V ¹³	
Orthopedic deformity	18/28 V ²³		10/28 V ²³
Trunk control		1/25 V ¹³	
Alertness	5/43 V ²¹		
Endurance	24/43 V ²¹		
Pain	13/43 V ²¹ 6/6 IV ²⁵		
Weight	6/43 V ²¹		
Functional Limitation/Activity			
Ambulating status	9/24 V ²²	3/24 V ²²	12/24 V ²²
Gait	20/24 V ²²	1/24 V ²²	3/24 V ²²
Walking	13/43 V ²¹		
Motor control (activities)	10/25 V ¹³ 31/43 V ²¹		
Oral motor control (activities)	13/43 V ²¹		
Transferring	13/43 V ²¹		
Overall function	20/24 V ²² 5/6 V ²⁵	2/24 V ²²	2/24 V ²² 1/6 V ²⁵
UE function	19/25 V ¹³		
Self care	14/43 V ²¹		
Positioning	33/43 V ²¹		
Sleeping	9/43 V ²¹		
Speech	11/43 V ²¹		
Disability/Participation			
Societal Limitation/Context			
Ease of care	4/6 V ¹³ 1/25 V ¹³	2/6 V ¹³	
School acceptance		4/6 V ²⁰	

Reduction of orthopedic deformity

One study, shown in Table IV, section 2, investigated effect of ITB on orthopedic deformity by measuring continued need for corrective surgery after 24 to 94 months of exposure to continuous infusion of ITB²³. It found that of 28 participants for whom surgery had been recommended before ITB began, surgery was no longer recommended in 18.

Limited joint range of motion is a sign of dynamic or fixed contracture which is one of the most common orthopedic deformities in CP. Direct measures of ITB on range of motion shown in section 1 were inconclusive; two reflected improvement, six were not statistically significant, and one reflected worsening. The single-subject study¹⁹ measured range of motion in the short term (finding improvement) and again in the long term (finding deterioration to below the original baseline)^c.

Strength

All five measures (see Table IV, section 1) showed reduced strength at both short- and long-term assessment, but these measures were made in a total of only three participants^{18, 19}.

Voluntary motor control

Two measures shown in Table IV, section 1 – one of upper extremity movement and one of lower, in the same participant – examined patterns of muscle activation and described an outcome composed of speed of movement, coordination, and accuracy¹⁹. Improved voluntary movement control was shown with ITB use by both measures. However, a third measure (speed of upper-extremity movement in two participants) showed no change¹⁸. Section 2 data show that trunk control worsened in one of 25 participants¹³.

Other aspects of impairment

All six participants in one study²⁵ and 13 of 43 participants in another²¹ experienced pain relief (see Table III, section 2). Improvements in endurance (24 of 43), weight (six of 43) and alertness (five of 43) were also reported in the latter study.

2. WHAT EVIDENCE IS THERE ABOUT ITB EFFECTS IN DIMENSIONS OTHER THAN IMPAIRMENT?

Pathophysiology

No human studies have investigated the physiology of ITB.

Functional limitation/activity

Data about function derived from group mean scores (see Table IV, section 1) included seven results of improvement in daily functioning, self-care, and/or activities requiring hand use and three results of unchanged function. Section 2 shows how individuals fared within the groups: 20 of 24 participants in one study rated their overall function improved, but two each perceived either an overall worsening or no change; five of six in another study improved with one unchanged. In other studies, 19 of 25 rated their upper-extremity function as improved¹³ and 14 of 43 rated self-care as improved.

^d (Personal communication, LA) Changes are also more likely to be statistically demonstrated in the lower than the upper extremities. The baclofen was injected into the lumbar cerebrospinal fluid which produces a lesser concentration of baclofen in the cervical region (approximately 1/4) than in the lumbar region.

^e A growth spurt accompanying puberty was suggested as a possible explanation for this change for the worse.

In regard to performance of gross motor activities, Table IV, section 1 results are split: three improved with ITB; four, were unchanged. In studies examining uniformity of effect (section 2), one found ambulatory status improved in nine in a group of 24, but three got worse, and 12 were unchanged²². A measure of gait in the same study showed that 20 improved, one got worse, and three were unchanged. In a different study, 13 of 43 reported their walking improved and 13 that their ability to transfer improved. Ratings of activities involving motor control improved in 10 of 25 and in 31 of 43 participants. For those with severe motor limitations, improved positioning was reported for 33 of 43.

For some individuals, there was improvement in activities involving oral motor control (13 of 43) and in speech (11 of 43). Finally, sleeping improved in 11 of 43.

Disability/participation

The only evidence about effect on social role participation was a single anecdotal report. Successful participation in a school fitness program was a positive outcome in one participant who won a 'most improved' award for fitness.

Societal limitation/context factors

There are three types of information about outcomes that have an indirect effect on the individual: caregiver burden, community caregiver acceptance, and financial cost. Caregiving was reported to be easier for four of six participants who experienced continuous infusion of ITB, but it was more difficult for the remaining two participants.

Four of six participants experienced lesser acceptance by school personnel^f. After pump implantation, their return to school was initially prevented because of concern about school staff's ability to handle medical complications that might arise with ITB use. Action had to be taken to overcome this resistance.

ITB was compared to another treatment for spasticity (selective posterior rhizotomy); ITB cost was found to be four times higher in the initial year of treatment, a negative in the dimension of societal limitations^g. In addition, ITB has ongoing costs including percutaneous refilling of the pump reservoir every 2 to 3 months and surgical replacement of the pump every 7 to 8 years. The relative efficacy of these two approaches has not been determined, however, and their use may have different indications.

3. WHAT COMPLICATIONS HAVE BEEN DOCUMENTED?

The longitudinal study by Almeida and coworkers of just one individual¹⁹ is exemplary in including outcome measures in multiple dimensions to specifically probe for linkages between impairment, functional limitation/activity, and disability/participation. Highlighting results from this study alone, it appears that reduced impairment, specifically the suppression of spastic signs (all eight results if upper-extremity muscle tone is excluded) together with improved quality of movement (both of two measures), may be linked with reduction in functional limitations (all eight results) and with greater ability for social role participation (a single result). Combining group mean results from the various studies, it also appears that reduced impairment, specifically the suppression of spastic signs (26 of 32 results) may be linked with improved function (14 of 21 results). This

limited evidence can only imply, however, that changes in the impairment dimension may affect changes in other dimensions.

4. WHAT KINDS AND MAGNITUDE OF COMPLICATIONS HAVE BEEN DOCUMENTED?

It is difficult to make meaningful statements about risks and complications from the published data that is summarized in Table V^h. Complications related to the catheter and pump seemed to occur with equal frequency as adverse outcomes. The mechanical complications were said to be minor and correctable although they required surgical intervention. Central nervous system side effects were documented in four studies despite the theoretical ability to avoid them by the smaller doses possible through intrathecal administration^{12, 20, 24, 25}. Somnolence and hypotonia were most common. Headache, nausea, and vomiting were also common. Infections and CSF leaks appeared to occur less often.

Some were serious complications. Two children contracted meningitis. Three were hospitalized for somnolence and hypotonia but did not experience respiratory failure.²⁴ Events of apnea, night-time hypotension, and bradycardia were reported in another study²⁰ which also reported a cardiorespiratory arrest occurring on a standard dose of ITBⁱ. These side effects were said to be neither dose dependent nor predictable.

Influence of ITB on seizure activity has been of concern. One study²⁰ reported three children having a single seizure during infusion. In another study²⁵, however, six participants were seizure-free over a 2-year follow-up. A third study to investigate ITB effect on seizures¹⁷, found no seizures in the 32 participants who had seizure-free histories. In the 19 participants in the study who were epileptic, nine seizures in 165 cumulative months of ITB were not regarded by the investigators as excessive given these participants' prior seizure histories.

5. WHAT IS THE STRENGTH OF THE EVIDENCE?

Strength of evidence depends on the number of people who have been studied, the consistency of findings across studies, and the internal validity of the body of evidence. Table III demonstrates that this body of evidence is limited to 14 studies, with an apparent total of 202 participants. There are known overlaps of participants between the studies by Armstrong et al.²⁰ and Steinbok et al.¹⁶, and between the studies by Krach et al.²¹ and Gilmartin et al.²⁴; this overlap can be calculated. The exact number of people who have been studied is clouded, however, because five other studies^{12-14, 22, 23} contain 137 participants from the Children's Hospital of Pittsburgh where a variety of studies

^f Personal communication, BA.

^g In 1995 Canadian dollars, the average cost of ITB was \$63 000, while SPR was \$16 900 per child with spastic quadriplegic CP up to 1 year after treatment. Much of the cost was said to be related to pump and catheter system complications.

^h The complete literature about ITB should be consulted for more extensive information about complications associated with ITB and their rates.

ⁱ A serious overdose is treated by intubation and ventilatory support, lumbar puncture to withdraw CSF, and emptying and temporarily turning off the pump.⁸ However, acute withdrawal of ITB has led to significant cardiorespiratory events. (Personal communication, BA)

were conducted over time, and the extent of overlap of people participating in these studies cannot be determined. Thus, the total number of individuals for which evidence is available is fewer than 202.

The strength of a body of evidence also depends on consistency of findings across studies. There is consistent evidence, based on group mean scores, that ITB suppressed signs of spasticity in the lower extremities (see Table IV, section 1). This suppression was clinically important and appeared to continue to improve over time. However, this

group evidence is weakened somewhat by the uniformity of effect data which shows that not all the participants demonstrated reduced muscle tone (see Table IV, section 2)^{12, 20}. This evidence is further confounded by the finding that there were also some participants with a positive response to the placebo^{24, 25}. Diminished strength is another consistent finding, but this evidence is limited to five measures made in only three participants (see Table IV, section 1). Otherwise, the treatment outcomes are inconsistent, singular, or known almost exclusively from anecdotal reports of uncontrolled observations (see Table IV).

Finally, credibility of results depends on methodologically robust research (see Table III). The levels of evidence indicate the extent to which the studies are more likely to inform than to mislead us. This body of evidence contains two studies that furnish relatively definitive Level I evidence about reduction of spasticity with bolus injections of ITB; one of these is an FDA-approved multicenter study. There is also positive Level II evidence about bolus injections from a small group study and about bolus injections as well as continuous infusion with an implanted pump from a study of a single participant. Other-wise, the research methodology of the overall body of evidence is relatively weak for several reasons. Only half of the 14 studies provided data that had been subjected to statistical analysis to calculate the probability of chance findings. Six of the studies required subgroup analysis to obtain data about participants with CP, and, in one study, those outcomes are referred to but not explicitly reported. Three-quarters of the research studies were capable of producing only Levels IV and V evidence with half of all the studies being Level V.

Table V: Adverse effects and medical complications (spasticity)

<i>Study</i>	<i>Type of effect</i>	<i>Events</i>
Albright ¹² <i>n</i> =23	Lethargy	1
	Disorientation and agitation	2
Albright ¹³ <i>n</i> =37	Urinary hesitancy	4
	Pedal edema	1
	Infections requiring pump removal and antibiotics	4
	Operations to correct catheter kinking, occlusion, breaks	5
Gilmartin ¹⁷ <i>n</i> =19	Seizure activity during ITB (people with prior seizures)	9
	Seizure activity during ITB (people without prior seizures)	0
Almeida ¹⁹ <i>n</i> =1	Operation to correct catheter break	1
Armstrong ²⁰ <i>n</i> =19	Sedation	1
	Bradycardia	2
	Hypotension	2
	Apnea	1
	Respiratory depression	1
	Meningitis	2
	CSF fistula persistent at catheter insertion site	1
Operations to correct pump and catheter system		10
	Seizure activity during ITB	3
Gerszten ²² <i>n</i> =24	Infection, pump related	1
	Catheter related issues	3
Gerszten ²³ <i>n</i> =48	Operations to correct catheter breaks or dislocations	11
Gilmartin ²⁴ <i>n</i> =51	Somnolence	18
	Hypotonia	31
	Headache	14
	Vomiting	14
	Nausea/vomiting	9
	Nausea	8
	Dizziness	6
	Increased salivation	6
	Pocket seroma	7
	Pocket infection	5
	Back pain at catheter site	2
	Cerebrospinal fluid leak	3
	Catheter dislodged	6
	Catheter break	2
Other device related events	34	
Van	Somnolence	1
Schaeysbroeck ²⁵ <i>n</i> =6	Catheter break	1
	Seizures	0

^j Each child had a history of seizures, but was stable and seizure free at the time of ITB infusion. (Personal communication, BA)

Part 2. Effects of ITB on dystonic CP

The primary use of ITB therapy in CP has been to decrease spasticity, but it has also been explored as a potential treatment for dystonic movement which can significantly impair function, be painful, and be difficult to treat. Dystonia is defined in these studies as frequent, involuntary, sustained muscle contractions that cause abnormal postures or twisting and repetitive movements. Many individuals with dystonia have significant cognitive impairments and are not expected to gain function; the goals of treatment in these cases is to accomplish improved comfort and easier care.

The mechanism of action of baclofen for dystonia is speculative, based on a theory of basal ganglia function and on the fact that individuals with secondary dystonia associated with CP often have lesions in the basal ganglia (in the striatum, usually in the putamen).²⁹ Putaminal lesions may reduce GABA-mediated inhibition of the external globus pallidus resulting in excessive stimulation of the supplementary motor cortex. Increased GABA levels may inhibit that excitation.

Summary and evidence tables

Six relevant studies were identified and are summarized in Table VI. (Details about the measures used as well clinical and statistical significance of each result can be found in the additional Summary of results table in the online version of this article on the Internet at www.aacpdm.org.) These results are aggregated here in Table VII. Complications and adverse effects are shown in Table VIII.

Analysis and discussion of evidence

1. WHAT EVIDENCE EXISTS ABOUT EFFECTS ON DYSTONIA AND OTHER IMPAIRMENTS?

Only 15 individuals with CP have been studied, but 12 had clinically important improvement in a short-term screening infusion (Table V). This included a reduction of facial grimacing, trunk arching, and other posturing. Ten of the people in whom improvement in dystonia was observed in a screening infusion continued into long-term therapy, but this improvement was maintained in only eight of them. However, dystonia worsened in one person immediately after a bolus injection. There was a resultant increase in dystonic movements of all limbs that persisted for 6 hours at which time treatment was stopped^k.

Other impairment outcomes were noted in two case reports. In both, the individuals appeared to be more comfortable. Scoliosis was unchanged after 18 months in one of these participants which may imply a positive effect, i.e. that scoliosis may have been arrested as a result of the ITB therapy³².

2. WHAT EVIDENCE IS THERE OF EFFECTS IN THE OTHER DIMENSIONS OF DISABILITY AND DO ANY LINKAGES EXIST FOR TREATMENT EFFECTS BETWEEN DIMENSIONS OF DISABLEMENT?

Two outcomes were also reported in the functional limitation/activity dimension. Positioning was more easily accomplished in two cases. Augmentative communication was unchanged in one case. Given the paucity of treatment outcomes, no speculation about linkages for treatment effects between dimensions can be made.

3. WHAT KINDS AND MAGNITUDE OF COMPLICATIONS HAVE BEEN DOCUMENTED?

In a total of 15 participants with dystonic CP, Table VIII indicates there was one complication of lethargy and three complications of infection (two meningitis)^l.

4. WHAT IS THE STRENGTH OF THE EVIDENCE?

This evidence is limited to four studies with a total of 15 people. Credibility is further limited by low ratings of the internal validity of the nine outcomes: seven Level V results (primarily

Table VI: Summary of studies (dystonia): intervention, participants, and research methods

Section 1. Intervention and subjects

Study	Treatment	Control	Participant characteristics	Total(n)	CP(n)	Age (y)
Narayan 1991 ³⁰	External pump		Life-threatening increase in dystonia upon spinal surgery age 18; prior generalized but predominantly axial dystonia with choreoathetosis and torticollis: static encephalopathy at birth.	1	1	18
Silbert 1992 ³¹	Single bolus injection (50µg dose)		Dystonia onset age 32 (no family history movement disorder); spastic quadriplegia CP and normal IQ: encephalitis at 18 mo.	1	1	33
Albright 1996 ³²	Internal pump		Severe, long term, generalized dystonia: 3 CP (2 with seizure disorder, 1 with MR), 2 Hallervorden-Spatz disease	5	2	7, 10
Albright 1998 ²⁹	Phase 1. External pump		Severe, generalized, painful, dystonia (none with significant spasticity; 3 with mild athetosis): 10 perinatal asphyxia,	12	11	4-42
	Phase 2. Internal pump		1 perinatal meningitis; 1 TBI	8	6 ^o	

^o CP numbers clarified by personal communication with MB.

Section 2. Research methodology

Study	Research design	Level of evidence	Duration of Rx	Nr in Rx group	Nr in control group	CP only results
Narayan ³⁰	Case report	V	14 mo	1	0	yes
Silbert ³¹	Case report	V	6 h	1	0	yes
Albright ³²	Case report	V	10 mo	5	0	yes
Albright ²⁹	Case series					
	Phase 1. Screening trial	IV	1 wk	12	0	yes
	Phase 2. Internal pump	IV	11-24 mo	8	0	yes

^k Narayan³⁰ reported a similar occurrence of worsening dystonia immediately after treatment via an implanted pump was begun. In that case, treatment was continued with dystonia improving and being controlled during the next several days and subsequently. More complete experience with ITB use in dystonia of all etiologies, however, suggests that worsening of dystonia is unusual; Albright has now screened about 100 people with dystonia and has not seen worsening in any, nor in the 85 who have been treated long term with pumps. (Personal communication, L Albright, March 2000).

^l Complete literature about ITB should be consulted for more extensive information about complications known to be associated with ITB technology and their rates.

anecdotal) and two Level IV. Only three outcomes were measured and only two of these were statistically evaluated.

Validity of the results is further called into question on the basis of measurement issues. Documenting the degree of dystonia is difficult, and consequently defining success from treatment is difficult. Assessing dystonia is particularly problematic in people with CP for a variety of reasons.²⁹ In addition to dystonia, they may have weakness, spasticity, lack of motor control, difficulty in communication, or cognitive disabilities. The first two case reports did not report how dystonia was assessed. The third study videotaped participants to assist in judging the effects of ITB on a simple rating scale. The last study employed the Fahn-Marsden dystonia movement scale to rate videotaped segments of the participants before and with ITB. However, the Fahn-Marsden scale, developed for rating dystonia associated with other diagnoses, had to be significantly modified because, in CP 1) dystonia is present both at rest and with volitional movement, and 2) most of the individuals are unable to perform the functional tasks on which the severity factors are based.

Summary and directions for future research

SPASTICITY

The body of evidence about ITB for spasticity in individuals with CP is still limited and, while promising, treatment effect has yet to be firmly established. This limited evidence shows that ITB reduced spasticity in the lower extremities, although effect on spasticity in the upper extremities was unclear. Function and ease of care improved. Medical complications were common, and while some were potentially serious, were manageable. Only a small and uncertain number of

people have been studied to date, however. Few outcomes beyond muscle tone have been measured more than once, and the research methodology employed in three-quarters of the available studies is not capable of confirming treatment effect. Clearly, further and more rigorous investigation is warranted.

Replication of the current findings in greater numbers of individuals needs to be undertaken. Our understanding of the value of ITB is most likely to be found within prospective, single-subject or group, randomized trials that use valid and reliable outcome measures in well described and homogeneous individuals. New studies need to report the uniformity of effect within groups (in screening trials and with implanted pumps) as well as group mean responses to ITB because factors that account for some but not all individuals having a response to ITB need to be explored.

The choice of outcome measures in new research should generate information pertinent to each domain of the NCMRR/WHO classification of disabilities. It is imperative that future studies extend what is known about outcomes beyond spasticity. This will allow the exploration of linkages to determine whether improvement in spasticity does carry over to improved movement control (within the impairment dimension), to improved functional skills or activities (in the dimension of functional limitation/activity), and to increased participation in the social roles of daily life (in the disability/participation dimension). Other factors outside the individual also need documentation (e.g. the value of treatment from caregivers' perspectives as well as any limitations society or other circumstances may impose on the treatment).

Greater understanding of other factors is also needed.

Table VII: Evidence table: state of knowledge about outcomes of treatment with ITB for dystonic CP based on evidence about uniformity of results.

The number of participants within a treated group (e.g. 9/11) that improved, worsened, and/or were unchanged is followed by a level of evidence (I to V) indicating the credibility of the result. The citation number for the study that produced the result follows.

<i>Outcome by dimension of disability</i>	<i>Positive results significant</i>	<i>Positive SS not evaluated</i>	<i>Negative SS not evaluated</i>	<i>Unchanged SS not evaluated</i>
Pathophysiology				
Impairment				
Dystonia	9/11 IV ²⁹ 6/8 IV ²⁹	1/1 V ³⁰ 2/2 V ³²	1/1 V ³¹	
Scoliosis				1/2 V ³²
Comfort		2/2 V ³²		
Functional limitation/activity				
Positioning		2/2 V ³²		
Communicating				1/2 V ³²
Disability/participation				
Societal limitation/context				

Table VIII: Adverse Effects or Medical Complications (Dystonia)

<i>Study</i>	<i>Type of complication</i>	<i>Nr of cases</i>
Albright ³²	Lethargy	1
	Pump related infection	1
Albright ²⁹	Infection: meningitis	2

Age or distribution of CP (i.e. spastic diplegia, hemiplegia, and quadriplegia) as well as ITB technology, including dosage and level of insertion of the catheter tip, may be important. Finally, systematic reports of complications (e.g. number of complications in relation to the total pump months) in this specific population must be provided to establish rates of adverse outcomes and facilitate risk/benefit analysis.

DYSTONIA

The evidence about ITB effects is only preliminary, but generally positive findings warrant more definitive investigation. Issues of description and assessment of dystonic CP must be addressed first, however. A standardized classification of CP is needed to allow for consistent diagnosis of dystonic CP, and a valid and reliable measurement scale is needed to document the degree of dystonia. The newly-published Barry-Albright Dystonia Scale (BAD) begins to address the latter need³³.

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