

RCT on intrathecal baclofen in dystonia

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Pediatric physiatrist

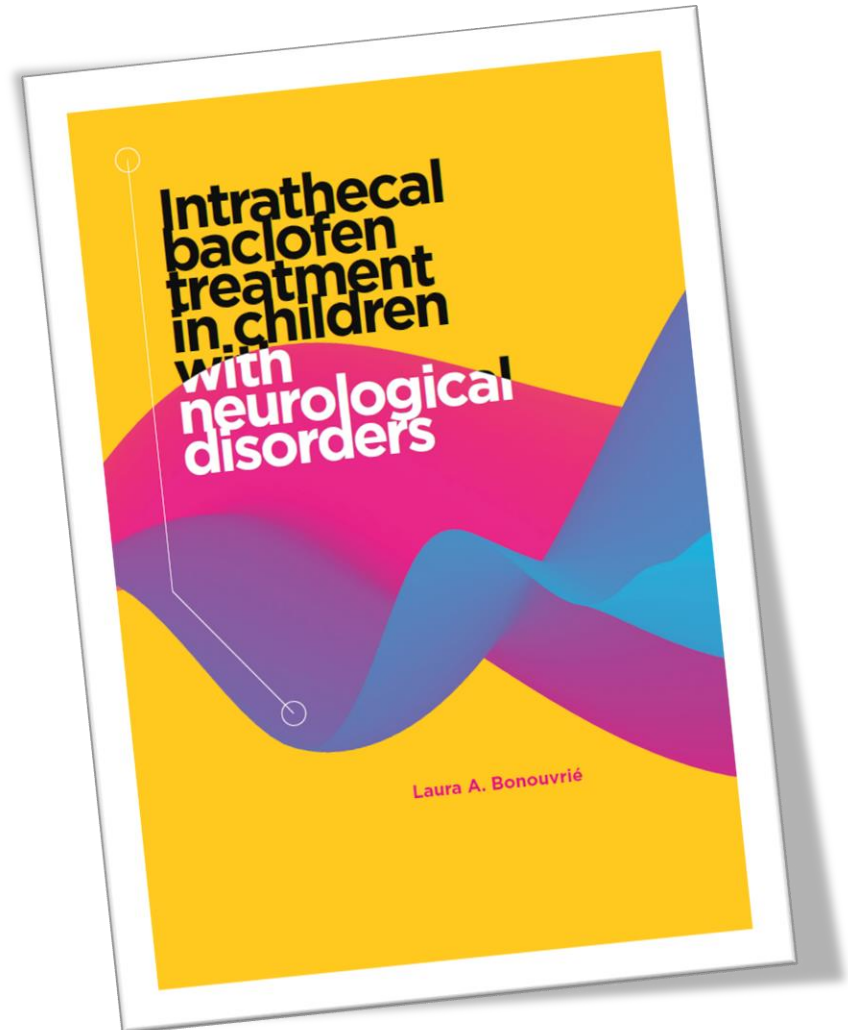
Amsterdam UMC, the Netherlands





Speaker

- Pediatric physiatrist since 2015
- Amsterdam UMC
- PhD okt 2019
- Network member:
 - European dyskinetic CP network (EDCPN)
 - Dutch group on movement disorders in children (LOBBK)
 - Centre of expertise CP (Amsterdam UMC)
- Focus
 - Complex care CP
 - Spasticity/dystonia





Q1 Who's in this webinar?



Learning objectives

By the end of the webinar you will be able to:

- Know the definition of dyskinesia in cerebral palsy
- Understand the hazards of RCTs in rare disease
- Identify patients with dystonia who might benefit from ITB

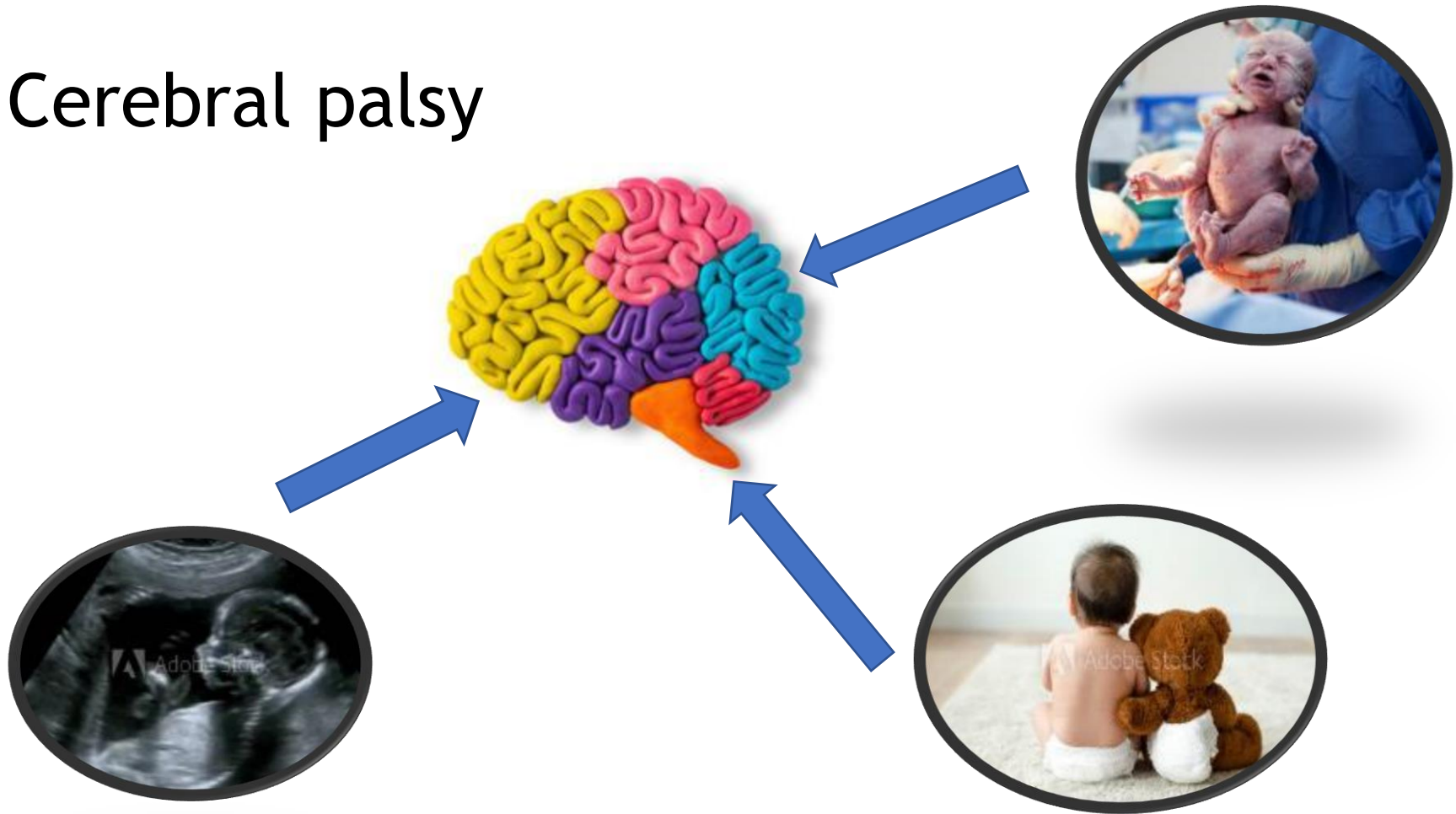


Webinar outline

- Background information and definitions
- IDYS trial
 - Why
 - How
 - Really how
 - Results
 - Conclusion
- The perfect future

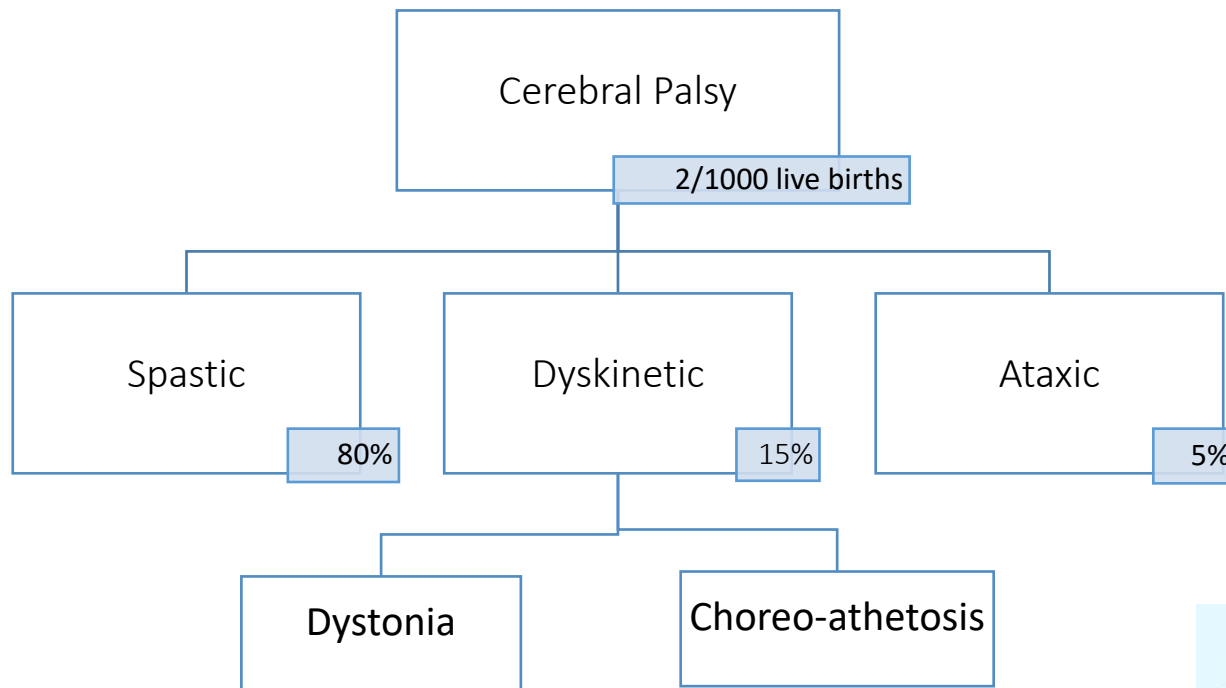


Cerebral palsy



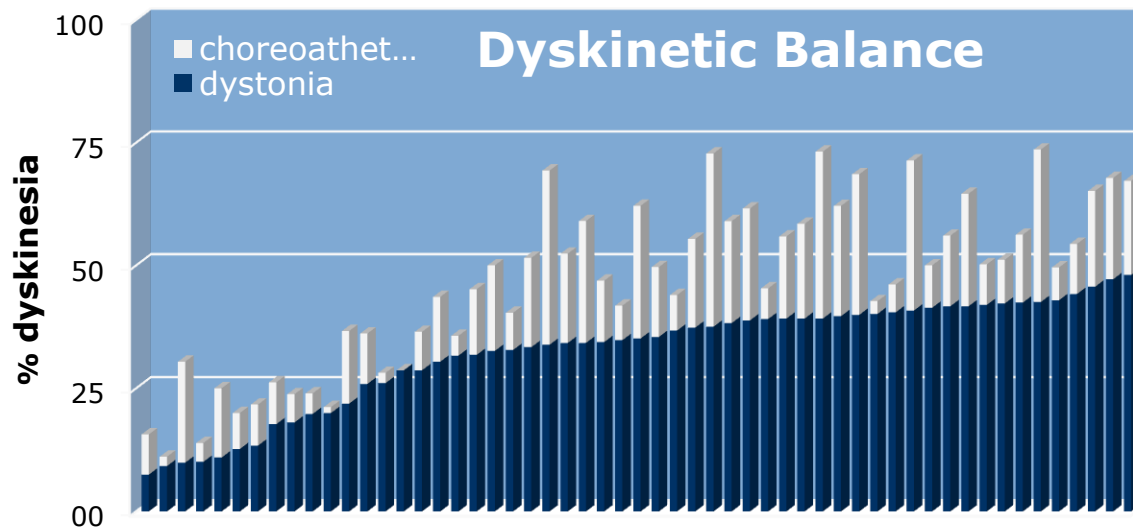


Movement disorders in cerebral palsy





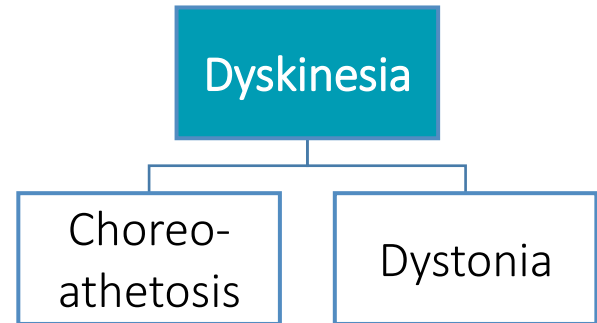
Dystonia vs Choreo-athetosis



Monbaliu et al. 2016 and 2017



Dyskinesia, definition



Involuntary, uncontrolled, recurring and occasionally stereotype movements with varying muscle tone

SCPE 2000, Rosenbaum 2007



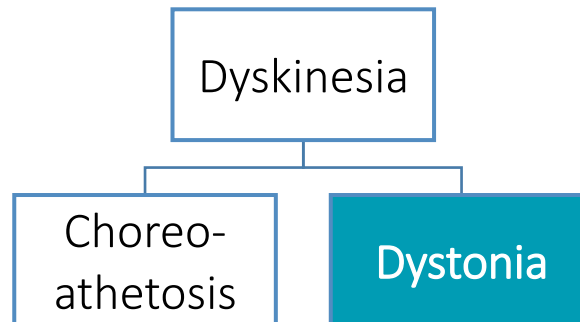
Monbaliu et al. Lancet Neurology 2017



Dystonia

Involuntary movements or intermittent muscle contractions that cause abnormal movements such as twisting and repetitive movements, and/or abnormal posture

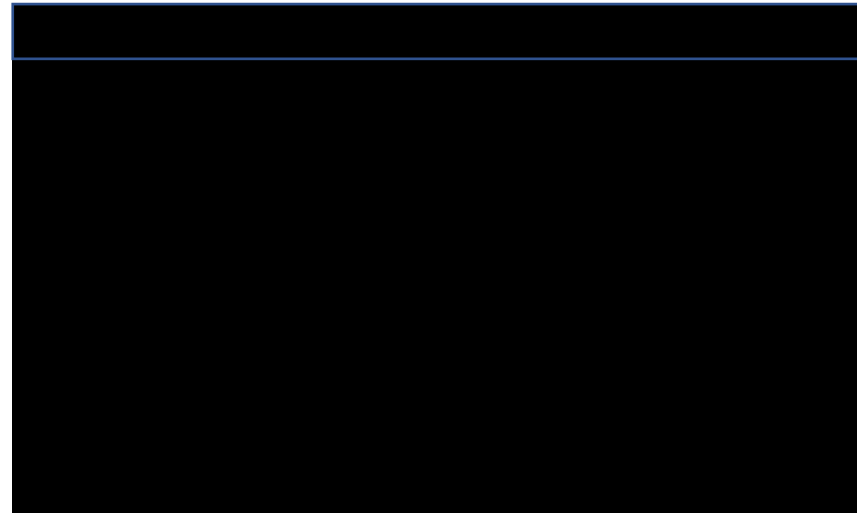
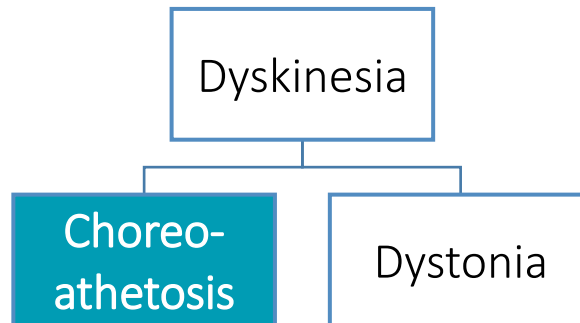
*Albanese et al (2013), SCPE (2000, 2007),
Sanger et al (2003, 2010)*





Choreo-athetosis

Ongoing, constantly changing ,
involuntary movements



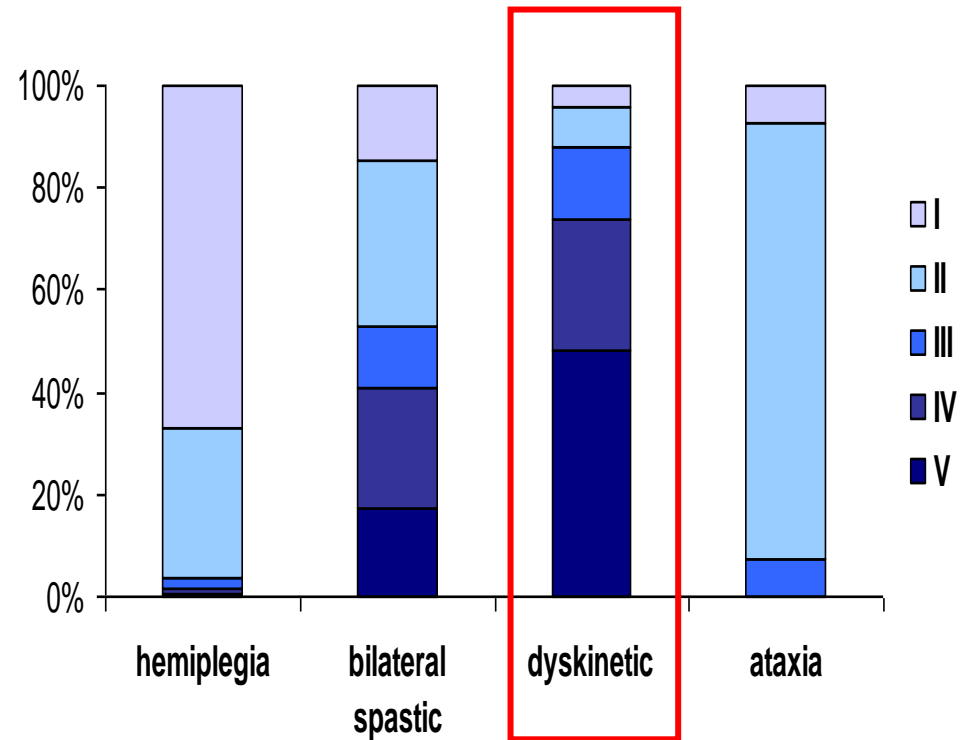


Dyskinetic Cerebral Palsy

- Mostly severe (GMFCS IV-V)

Monbaliu E et al. 2017, Himmelmann et al 2006

- Treatment goals:
 - Care giving
 - Transfers/sitting
 - Comfort
 - Contractures



⁴Himmelmann et al 2006



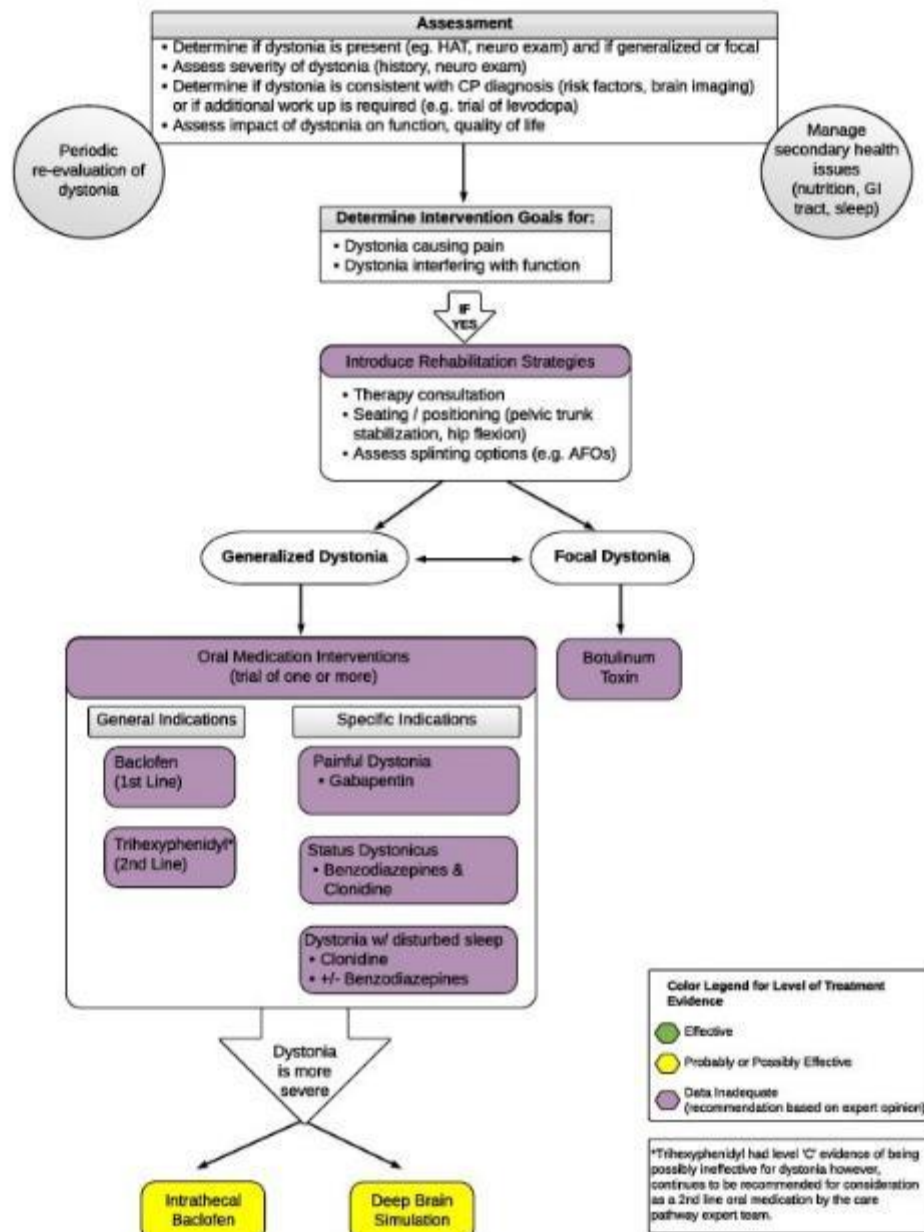
Q2 which treatment options for severe dystonia do you use?

Multiple answers possible

- Oral medication such as baclofen or trihexyphenidyl
- Botuline toxine
- Deep brain stimulation
- Intrathecal baclofen
- Orthopedic surgery (muscles)
- Orthopedic surgery (bones)

Treatment options dyskinetic CP

Monbaliu et al. 2017; Fehlings 2018







Intrathecal baclofen (ITB)





The Effect of Intrathecal Baclofen in Dyskinetic Cerebral Palsy: The IDYS Trial

Laura A. Bonouvrié, MD ¹, Jules G. Becher, MD, PhD,² Johan S. H. Vles, MD, PhD,³
R. Jeroen Vermeulen, MD, PhD,^{3,4†} and Annemieke I. Buizer, MD, PhD ^{2†}
on behalf of the IDYS Study Group

ANN NEUROL 2019;86:79–90

A multi-center, randomized double blind, placebo controlled trial



Cerebral Palsy Center of Expertise



Aim

Evidence for the effect of ITB on:

1. Individual treatment goals
2. Dystonia, spasticity, range of motion, pain, comfort and treatment related complications



Methods

Patients

Inclusion criteria

- Aged 4 to 25
- Dyskinetic CP
- GMFCS IV or V
- Lesions on MRI
- Eligible for ITB (using criteria of common practice)





Eligible for ITB

criteria of common practice

1. The etiology is preferably known;
2. Management of aggravating factors, such as pain and discomfort, should be optimal;
3. Other treatment options should have been explored.
4. The movement disorder should be so severe that it interferes with activities of daily life or quality of life;
5. Treatment goals should be clear and applicable and, to avoid disappointment, it is important that patients and parents understand these goals;
6. Patients and parents should be motivated and able to adhere to the requirements of treatment,
7. Patients should have sufficient body size to allow pump implantation



Methods

Design

Multi-center, randomized double blind, placebo controlled trial

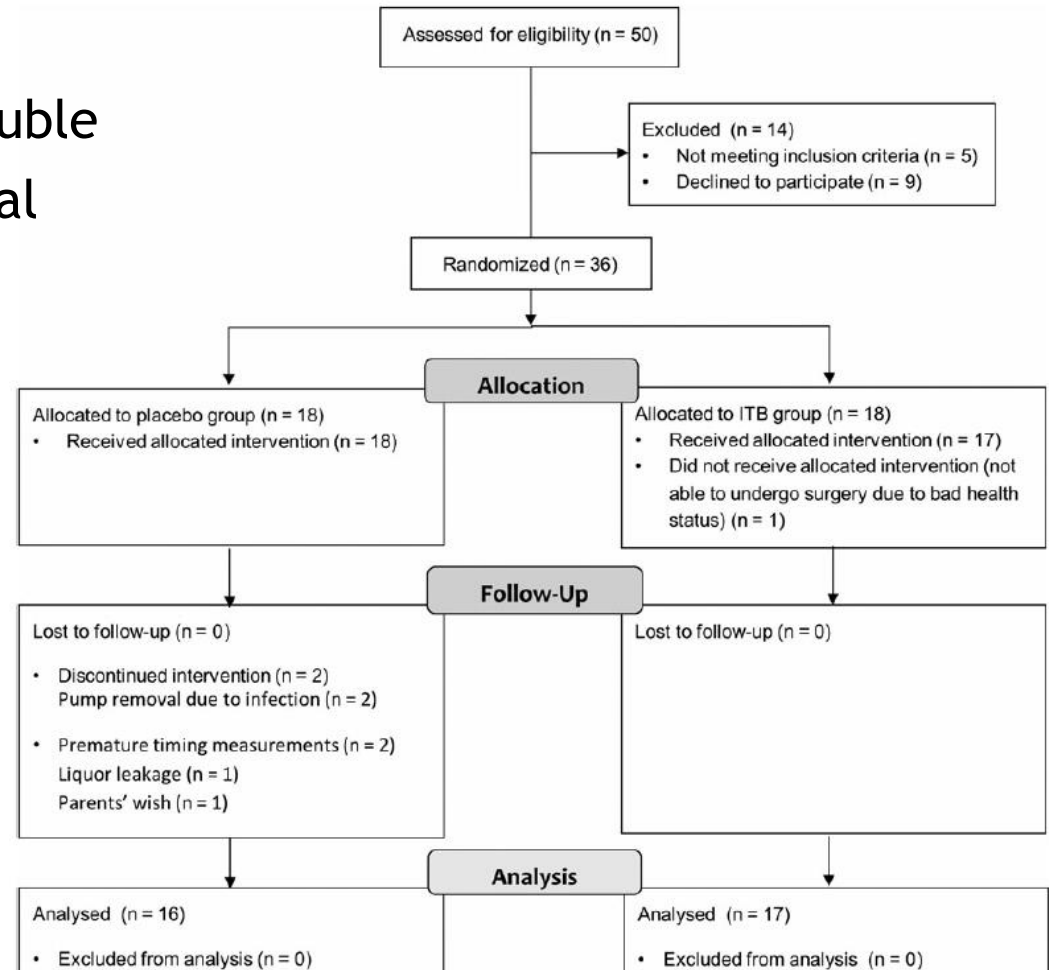


FIGURE 3: Trial profile. ITB = intrathecal baclofen.



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Planning, the aims

- Start nov 2009 -> protocol, MEC, funding
- Inclusion 1^e patient jan 2013
- Inclusion period 2,5 years
- 30 patients
- Eligible patients had the choice weather to participate
- Or not....



How it really went (1)

- Start inclusion jan 2013

Problem 1

- Low inclusion number
 - 4 in 1 year
- Data safety monitoring board & MEC
 - > experimental treatment -> only in trial
 - > extension inclusion period



How it really went (2)

Problem 2

- Complications
 - In which group?
- Data safety monitoring board & MEC
 - > inclusion to 36 patients
 - > longer inclusion period

Last measurement july 2018 (5,5 years)



Methods

Primary outcome measure



Goal Attainment Scaling

Individual goals

Standardized score (GAS T-score)

Statistics



Methods

Primary outcome measure

12 year old boy

Problem: wants to sit in his wheelchair for a longer period of time

-3	worsening	19 minutes or less
-2	Baseline / no change	20-30 minutes
-1	Improvement (goal not achieved)	31-59 minutes
0	Goal achieved	60 minutes
+1	More than goal achieved	61-75 minutes
+2	Much more than goal achieved	76 minutes or more



Methods

Secondary outcome measures

- Dystonia
 - Barry Albright Dystonia Scale
 - Dyskinesia Impairment Scale
- Spasticity
 - H-reflex
 - SPAT
- Range of motion
- Comfort (VAS)
- Pain (VAS)
- (serious) adverse events



Methods

Secondary outcome measures

- Dystonia
 - Barry Albright Dystonia Scale
 - Dyskinesia Impairment Scale

- 8 body regions
- 5 point scale
 - None to severe
- Score range 0 - 32



Methods

Secondary outcome measures

- Dystonia
 - Barry Albright Dystonia Scale
 - Dyskinesia Impairment Scale

- 12 body regions
- Dystonia and choreo-athetosis
- Rest and activity
- Duration and amplitude
- 5 point scale
- Score range 0-100%



Results

Primary outcome measure



Goal Attainment Scaling

- Care giving
 - Washing / dressing / hygienic care
- Mobility
 - Transfers / sitting
- Body functions/structures
 - Comfort/pain
 - Sleep
- Communication

Results

Primary outcome measure



Goal attainment scaling - GAS T-scores

	Placebo (n=16)		ITB (n=17)		Regres. Coef. (95%CI)	Effect size (Beta)	p value
	Baseline	3 months	Baseline	3 months			
GAS T-score	n.a.	21·0 (SD 4·6)	n.a.	38·9 (SD 13·2)	17·8 (10·4 to 25·0)	0·672	^{^^} 0·00

^{^^}Linear regression analysis.

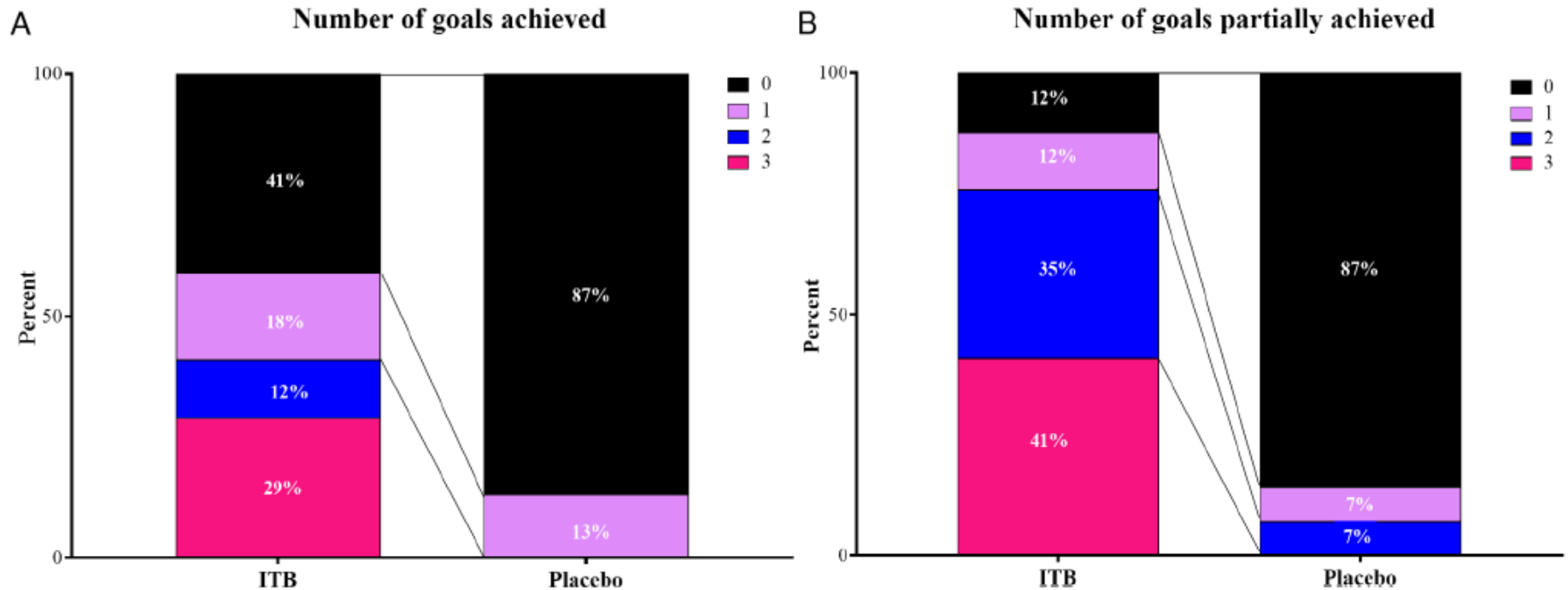
- No change: 22.5-25.0
- All goals attained: 50



Results

Primary outcome measure

Goal attainment scaling - nr of goals





Results

Secondary outcome measures

Barry Albright Dystonia Score

	Placebo (n=16)		ITB (n=17)		Regres. Coef. (95%CI)	Effect size (Beta)	p value
	Baseline	3 months	Baseline	3 months			
BADS	20.6 (8.9)	19.1 (5.9)	19.9 (7.5)	20.4 (4.4)	-1.50 (-4.9 to 1.9)	-0.3146	^{^^} 0.38

Data are presented as mean (SD). Regres. Coef.=Regression Coefficient. ^^Linear regression analysis.



Results

Secondary outcome measures

Dyskinesia impairment scale

		Placebo (n=16)		ITB (n=17)		Regres. Coef. (95%CI)	Effect size (Beta)	p value
DIS	Dystonia	Baseline	3 months	Baseline	3 months	-9% (-16% to -2%)	-0.34	^^0.013
		65% (17%)	73% (9%)	67% (11%)	64% (16%)			
	Choreo-athetosis	16% (17%)	16% (20%)	21% (15%)	15% (13%)			+0.77

Data are presented as mean (SD). Regres. Coef.=Regression Coefficient. DIS= Dyskinesia Impairment Scale. ^^Linear regression analysis.



Results

Secondary outcome measures

- Spasticity
 - H-reflex
 - MAS
- Pain (VAS)
- Comfort (VAS)
- Range of motion
- (serious) adverse events

No significant difference



Key points/ conclusion

- Level II evidence
- Individual treatment goals are attained more with ITB than with placebo
- Trials with rare disorders/treatments take a lot of time (and effort)
- Future perspectives
 - Long term effects - 1 year
 - Measures for success?
 - Collaborations/networks

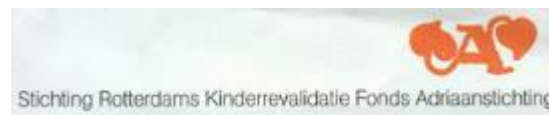




Team work



Cerebral Palsy Center of Expertise





Co-financed by the Connecting Europe Facility of the European Union



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Neurological Diseases
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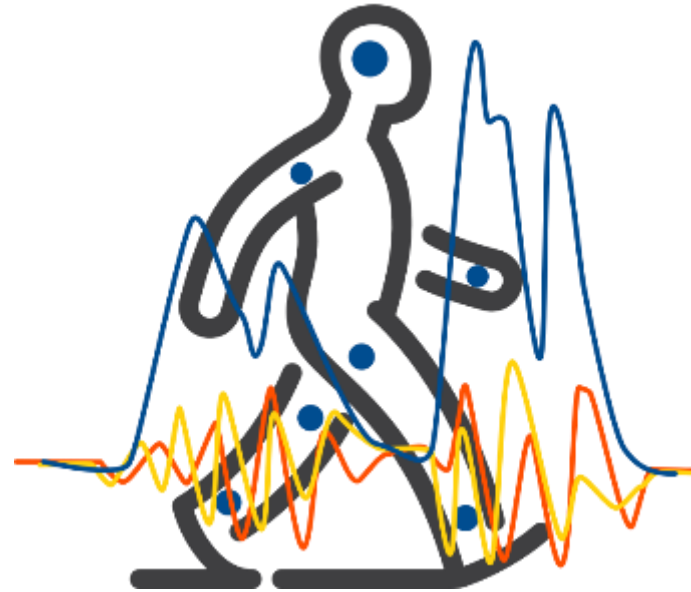
30. June 2020



Neurological Diseases
(ERN-RND)

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Joint webinar series



THANK YOU

Next Webinar: ‘Environmental modifiers in
Hereditary Spastic Paraplegia‘

9. July 2020, 15-16h CET