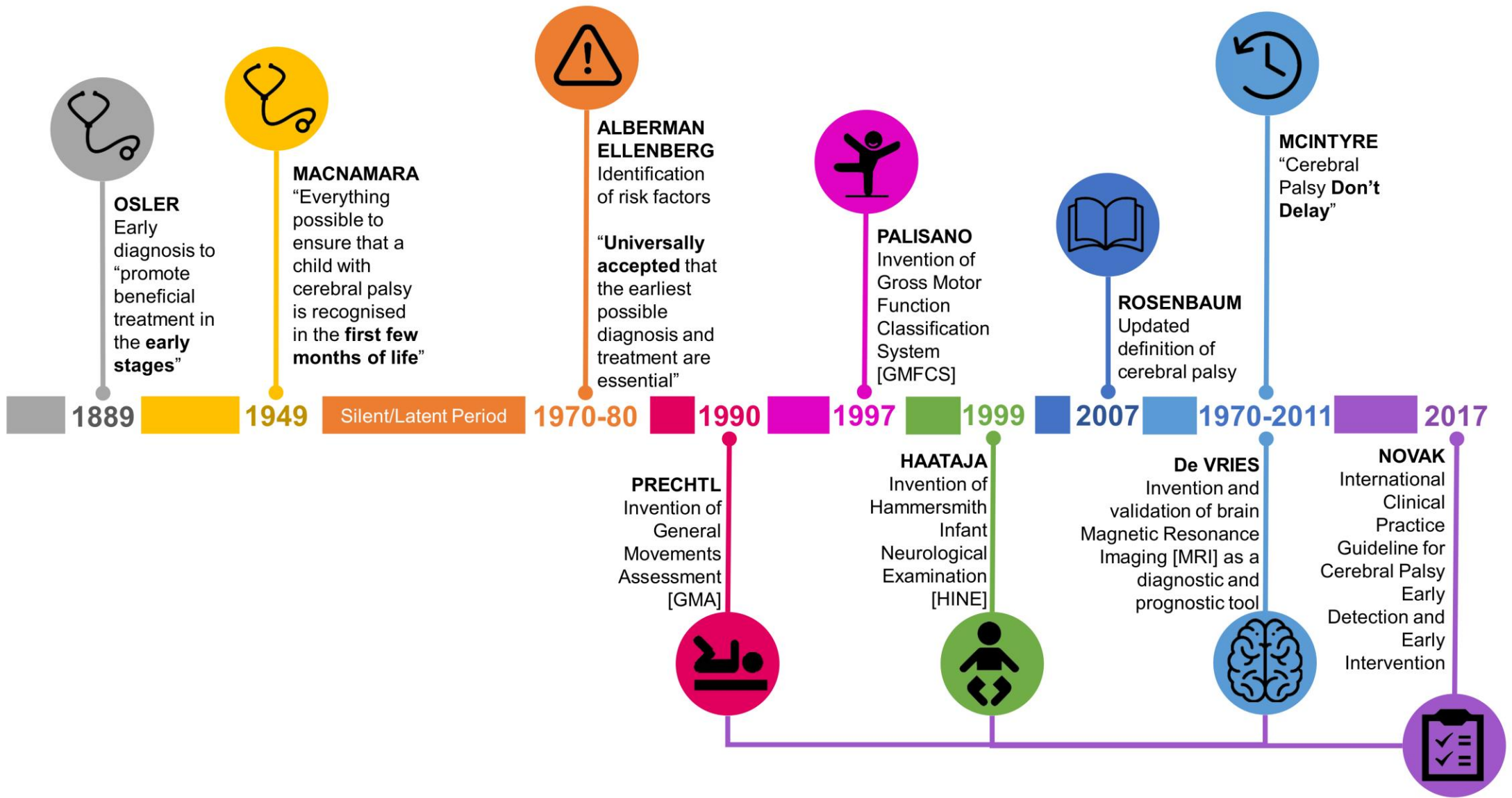


Pregled novosti pri obravnavi otrok in mladostnikov s cerebralno paralizo

Doc.dr. Tina Bregant, dr.med., spec. pediatrije, spec. FRM
CIRIUS Kamnik

7. STROKOVNO SREČANJE V CIRIUS KAMNIK
19.11.2021





te Velde, Anna, Catherine Morgan, Iona Novak, Esther Tantsis, and Nadia Badawi. 2019. "Early Diagnosis and Classification of Cerebral Palsy: An Historical Perspective and Barriers to an Early Diagnosis" *Journal of Clinical Medicine* 8, no. 10: 1599.

<https://doi.org/10.3390/jcm8101599>

CP

- Heterogena skupina (redkih) stanj s stalno gibalno oškodovanostjo, ki se kaže v spremembah miš. tonusa, drže ali/in gibanja.
- Nenapredujoče okvare razvijajočih se možganov (pre/peri/post natalno)
- Spreminjajoča se klinična slika pogojena z razvojem, rastjo, staranjem
- Omejitev funkcionalnosti
- Oškodovanost: gibalna/zaznavna/intelektualna/govorno-jezikovna/vedenjska + paroksizmalne motnje (epilepsija), mišično skeletne težave.



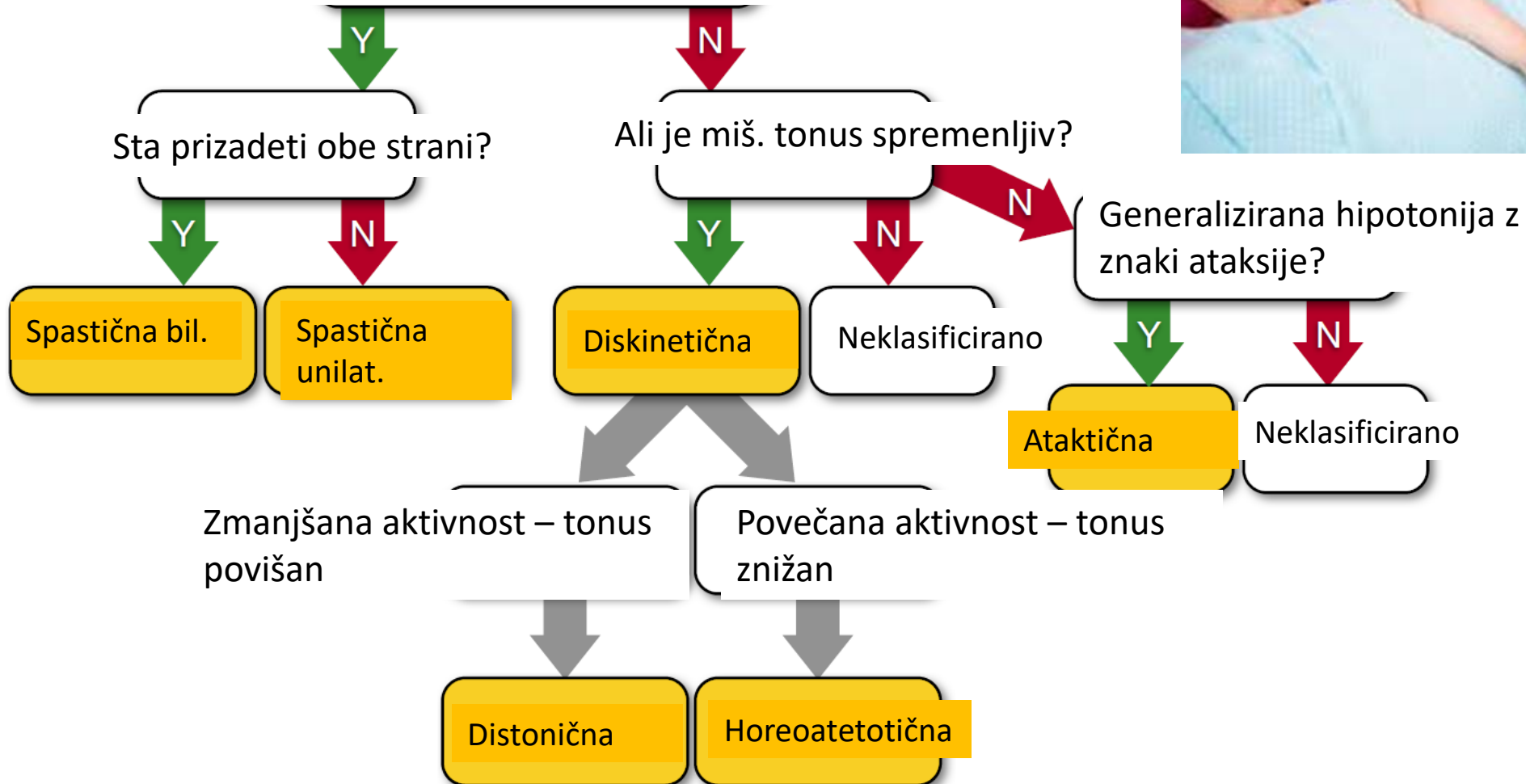
Cans C. (2000). Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. *Dev Med Child Neurol*, 42: 816-824. doi:10.1111/j.1469-8749.2000.tb00695.x.

Cans C, Dolk H, Platt MJ, et al. (2007). Recommendations from the SCPE collaborative group for defining and classifying cerebral palsy. *Dev Med Child Neurol*, 49: 35-38. doi:10.1111/j.1469-8749.2007.tb12626.x.



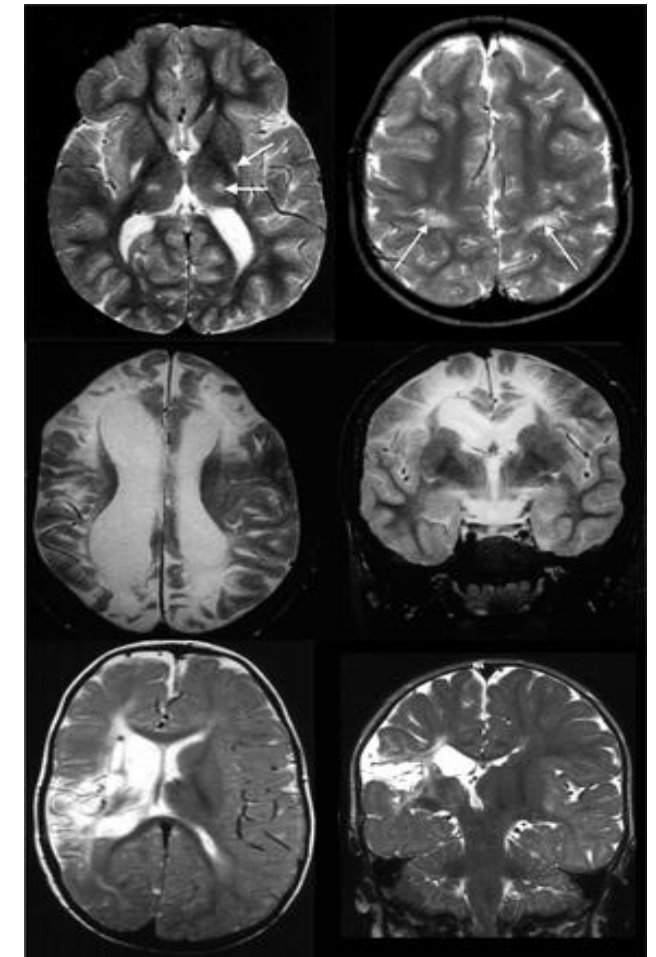
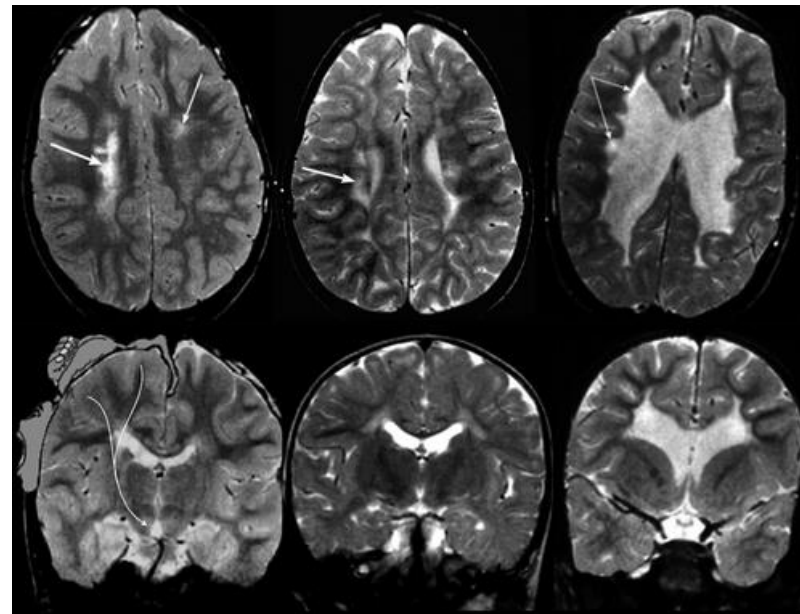
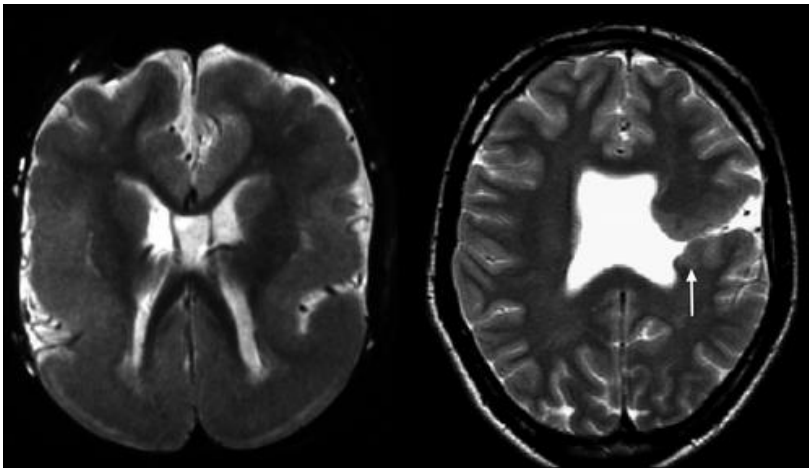
KLASIFIKACIJA CP

Ali je miš. tonus povišan
v enem/več udih?



Vzročna diagnostika -> Th.

- Malformacije (A kategorija) 1. in 2. trimester	11%	ataksija	Lisencefalija
- Poškodba beline (B kategorija) zgodnji 3. trimester + nedonošenčki	49%	spast. uni/bilat, diskin	PVL
- Poškodba sivine (C kategorija) pozni 3. trimester, pred/po rojstvu	21%	spast. uni/bilat, diskin	BGT/C+SC lezij /MCAinfark
- Razno (D kategorija)	8,5%	ataksija	
- Normalen MR (E kategorija)	10,5%	ataksija	



Terapija/obravnave v Slo (RA, Cirus, drugi zavodi, URI Soča)

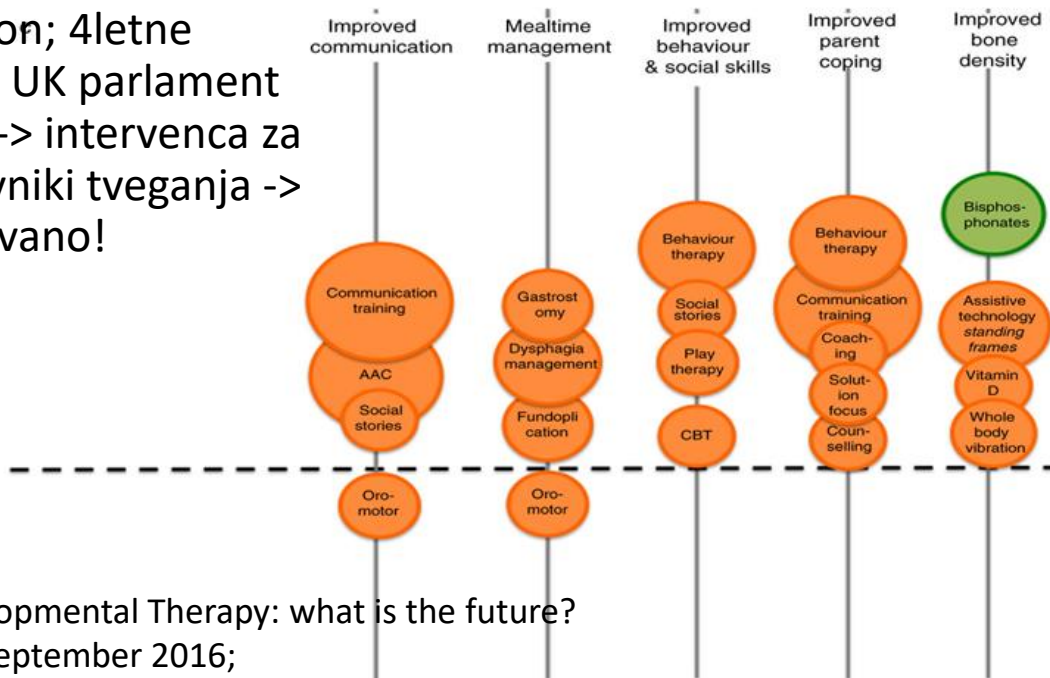
- Nfth
- DT
- Logoped
- Vključenost v šport, igralne urice – spec. pedagog
- Soc. delavec
- Psiholog
- Vodja tima: zdravnik: razvojni pediater/fiziater

- Ortotika, MTP
- Okulist
- Prehrana (dodatki + preventiva tihih aspiracij)
- Urinska inkontinenca

- Zdravila:
- Proti spastičnosti: Btx, AEZ, Baklofen, Diazepam
- Preventiva: th osteoporoze (vit D, CaCO₃, bifosfonati), preprečevanje okužb (cepljenja: gripa, pnevmokok, sars-cov-2!)
- Motnje spanja: Melatonin (Slenyto)
- Th slinjenja: (obliži Scopoderm, Robinul, Btx lok.,)
- Th zaprtja: (Lactecon, Macrobalans, prehrana, pitje)
- Th. Bolečine: fizikalno + PBZ + nevropatska bol. - pregabalin (Lyrica)

„Klasična obravnava“

- RNO
- **Bobath:** Bertha & Karel Bobath, London; 4letne čakalne vrste; UK parlament potrdil 1965 -> intervencija za otroke z dejavniki tveganja -> 2013 odsvetovano!

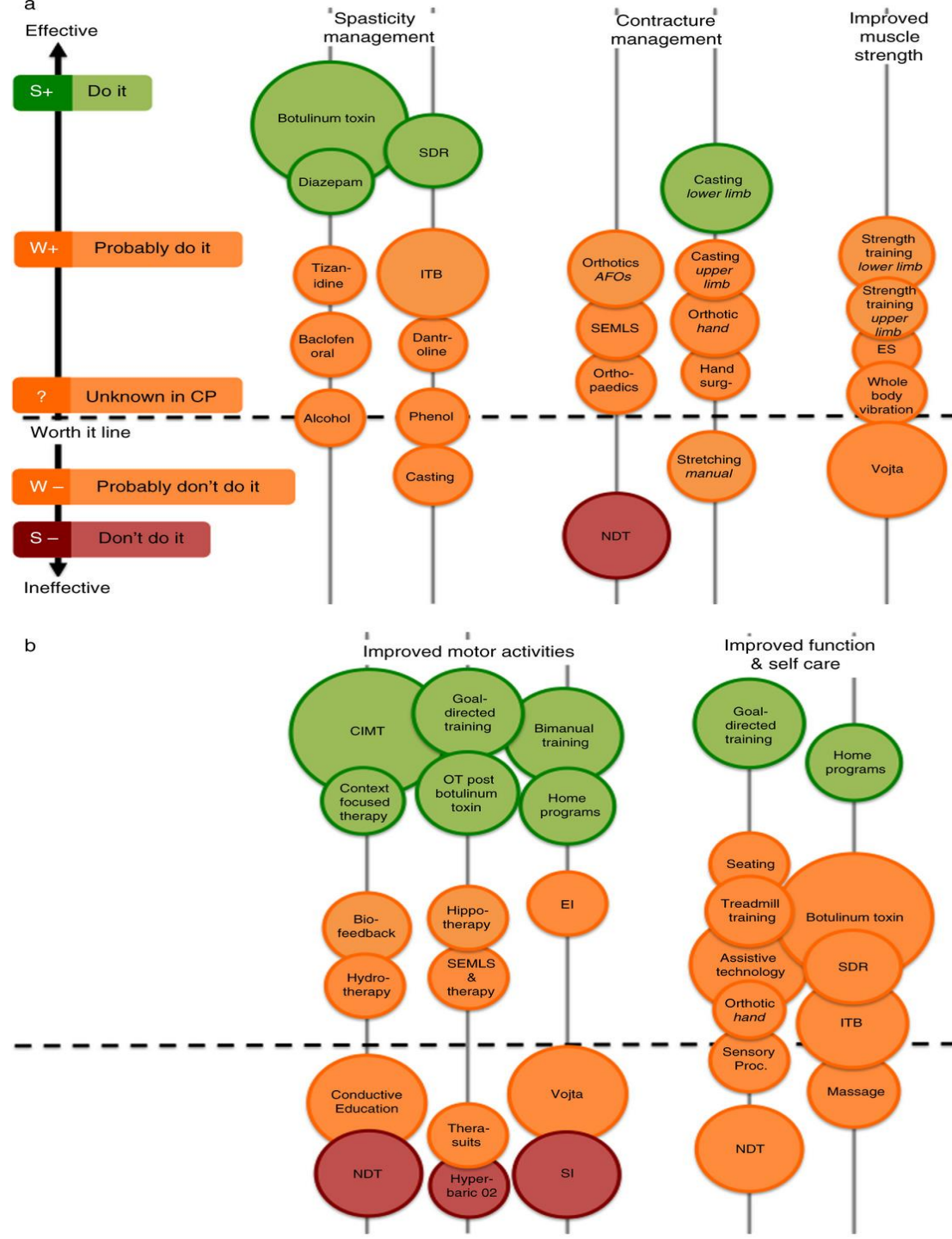


Bobath and NeuroDevelopmental Therapy: what is the future?

Margaret Mayston; 02 September 2016;

<https://doi.org/10.1111/dmcn.13221>

Novak I, McIntyre S, Morgan C, et al. A systematic review of interventions for children with cerebral palsy: state of the evidence. Dev Med Child Neurol 2013; 55: 885–910.



Ortopedske & Fiziatrične intervence

- Ortopedske krg. (podaljšava tetiv, sprostitve kontraktur, op. kolkov, stopal,...) – različne tehnike (npr. Ulzibat?!)
- Mavčenje
- Uporaba botulinum neurotoxin A (tudi za drobne mišice obraza, požiranja)
- MTP (ortoze, komunikatorji, iv,...)
- Usmerjen trening, CIMT
- Hipoth, Halliwick, Vaje za moč,...
- SDR
- Krg. Skolioze
- Krg. inkontinence

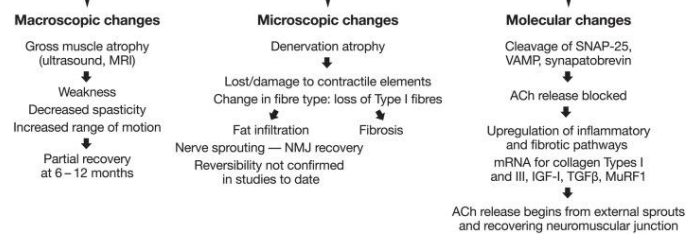
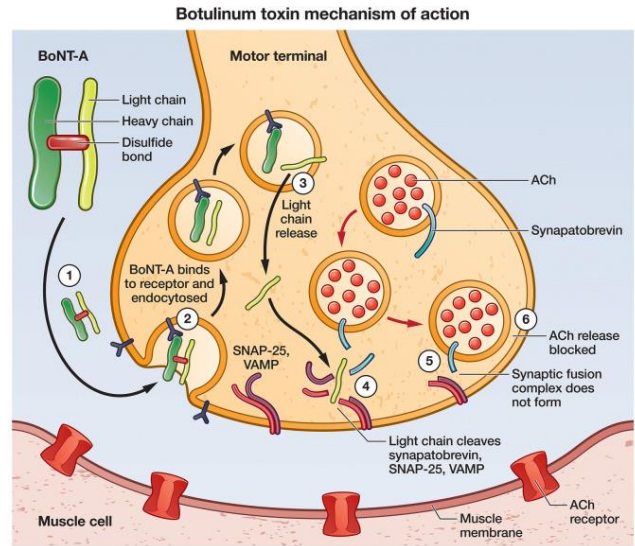
Botulinum toksin A

Znižuje mišični tonus pri otrocih s CP
 Izboljša kratkoročno držo in hojo
 Varno
 Toda na račun mišične atrofije, ki ni nujno reverzibilna

Lokalna reakcija/sistemska pri nehodečih

Revizija protokolov

BoNT-A -> podaljšava tetiv



Stage

1

**Spasticity
Dynamic
contracture**

- Physical therapy
- Orthotics
- Botulinum neurotoxin A

2

**Fixed
musculotendinous
contracture**

- Muscle recession
- Tendon lengthening

3

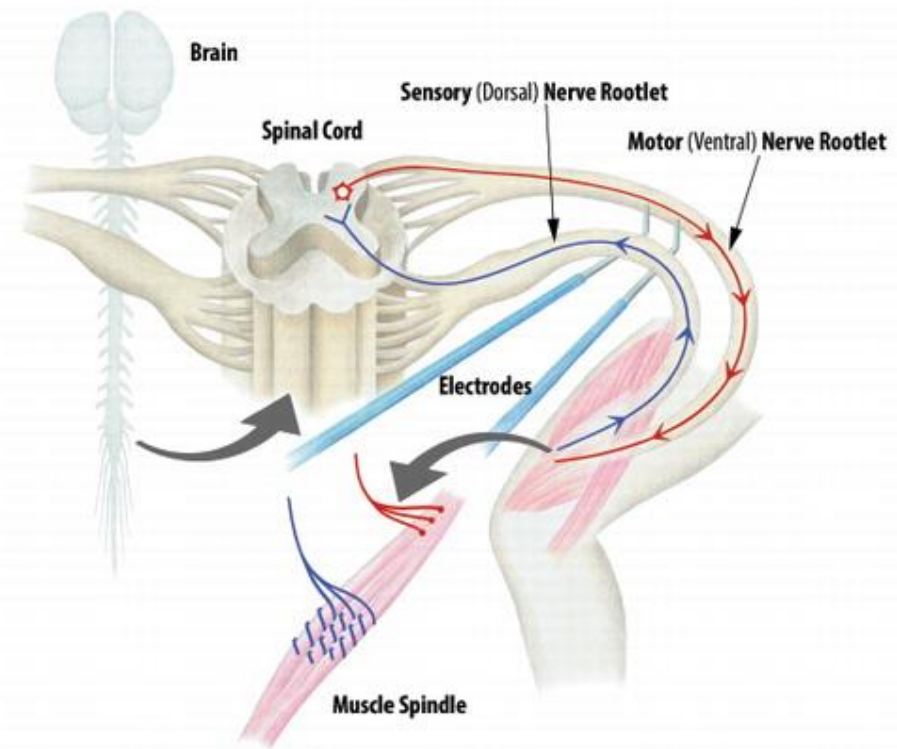
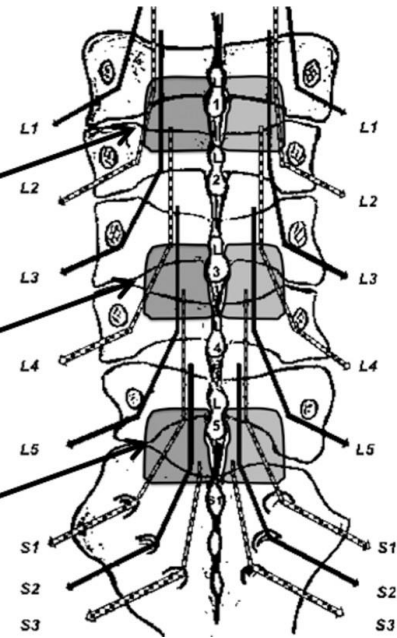
**Contractures and
bony torsion or
joint instability**

- Muscle-tendon surgery
- Rotational osteotomies

SDR

Harmful Spastic components

- Hip Flexion**
Psoas (L2)
Thigh Adduction
Adductors (L3)
Access to L2/L3
- Extended Knee & Patellar ascension**
Quadriceps (L4)
Access to L4/L5
- Knee Flexion**
Hamstrings (L5/S1/S2)
Foot Equinism – Varus
Triceps surae – Tibialis posterioris (S1)
Flexor digitorum - bladder (S2)
Access to S1/S2



<https://www.youtube.com/watch?v=pH3qvgFvJ9U>

What has NICE said?

The evidence shows that the procedure is effective but that complications can be serious. This procedure can therefore be offered routinely as a treatment option for spasticity in cerebral palsy provided that doctors are sure that:

- the parents or carers understand what is involved and agree to the treatment, and
- the results of the procedure are monitored.

Parents or carers should be told that the procedure cannot be reversed, that walking ability and bladder function may deteriorate, and there may be later problems, such as spinal deformity. They should understand that prolonged physiotherapy and aftercare will be needed and that additional surgery may be necessary.

A healthcare team with specialist training and expertise in the management of spasticity in cerebral palsy, with access to the full range of treatment options, should decide which patients could benefit from this procedure and should carry it out. The team would normally include a physiotherapist, a paediatrician and surgeons.

NICE has encouraged further research into this procedure.

SDR

- Nerandomizirana primerjalna raziskava No=142; SDR (n = 71) vs intratekalna Baklofenska črpalka (ITBP) (n = 71): MAS (0-5): -2.52 vs. -1.23 točke 1 leto kasneje (p < 0.0001); starši zadovoljni v 94% in 96%
- Nerandomizirana primerjalna raziskava No=108 Nfth + SDR vs. Nfth: GMFM 87 na 92 in 89 na 91 20-mes kasneje (za obe skupini p < 0.05).
- **Delfi: manjša spastičnost v sp. udih; manj ortopedskih posegov, višji GMFM, boljša drža in hoja, večja samostojnost, boljša QoL**
- Študija primerov No=208 - skolioza ob laminektomiji v 9% (5/58) in ob laminoplastiki 1% v 4 letih
- Študija primerov No=105, 98, 30 skolioza >10° v 55% čez 4.3 years, 43% čez 5.8 years; skolioza > 35° v 50% čez 21.4 let
- Študija primerov No=61 - 4 spondylolysis + grade-I spondylolisthesis 3-5 let po proceduri
- Študija primerov No=208 - retenca urina + hyporeflexia v 10% (20/208); 18 se je popravilo v 4 tednih; 2 s stalno urinsko inkontinenco in atoničnim mehurjem
- **Delfi: smrt, poslabšanje motorične funkcije/paraplegije; okužba rane, meningitis, CSF fistule, dislokacija kolcev, bolečina v križu, zaprtje, šibkost, kronična bolečina, pozni arachnoiditis ali/in syringomyelia**

Baklofenska črpalka

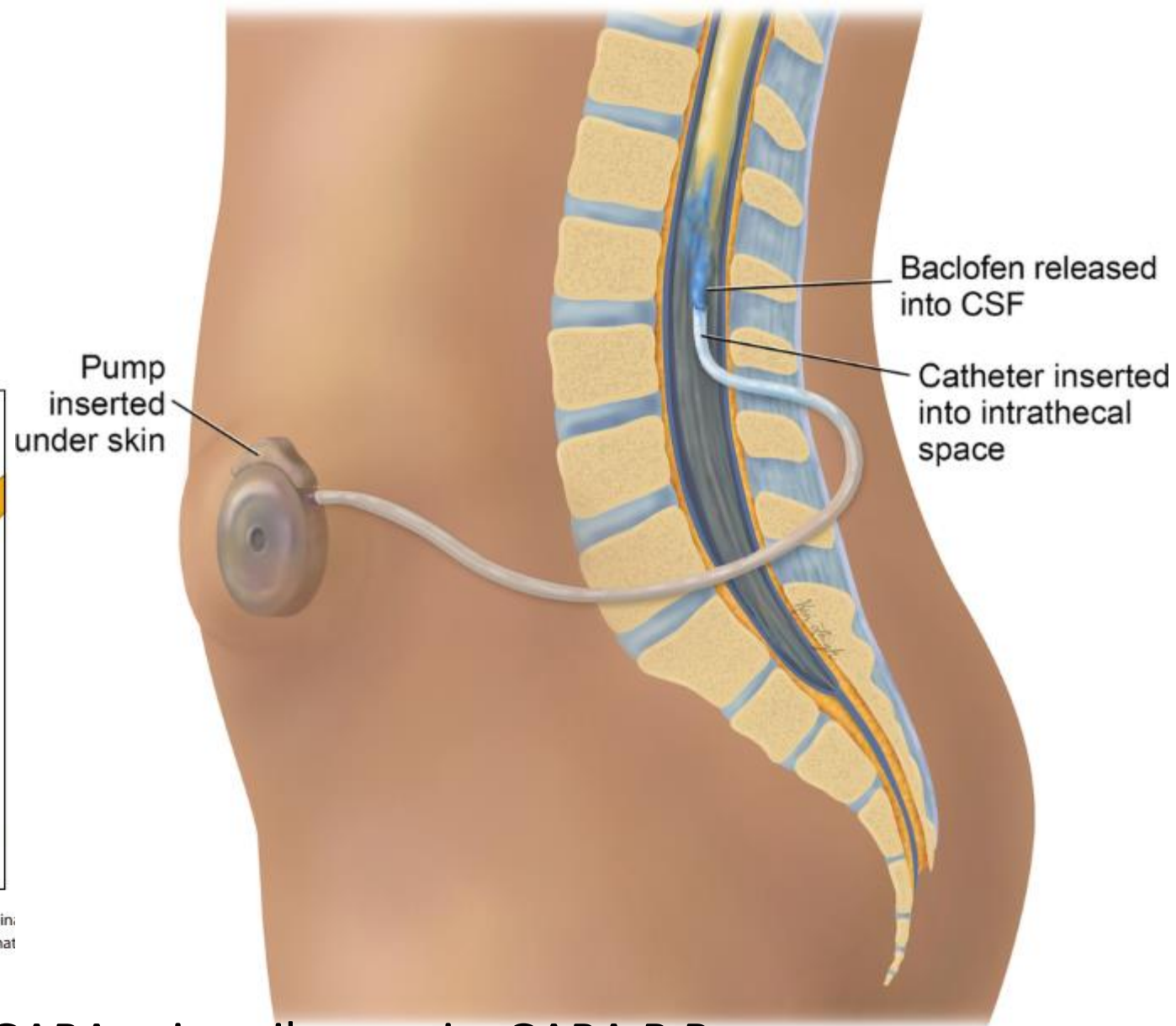
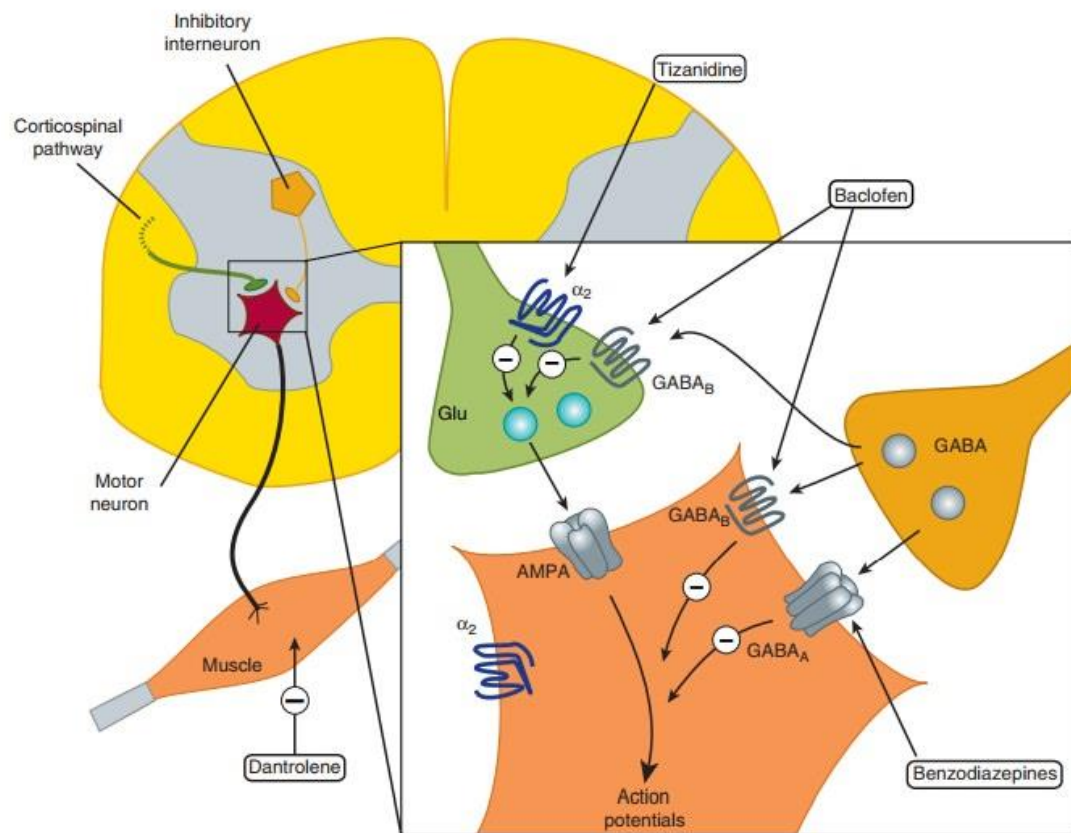
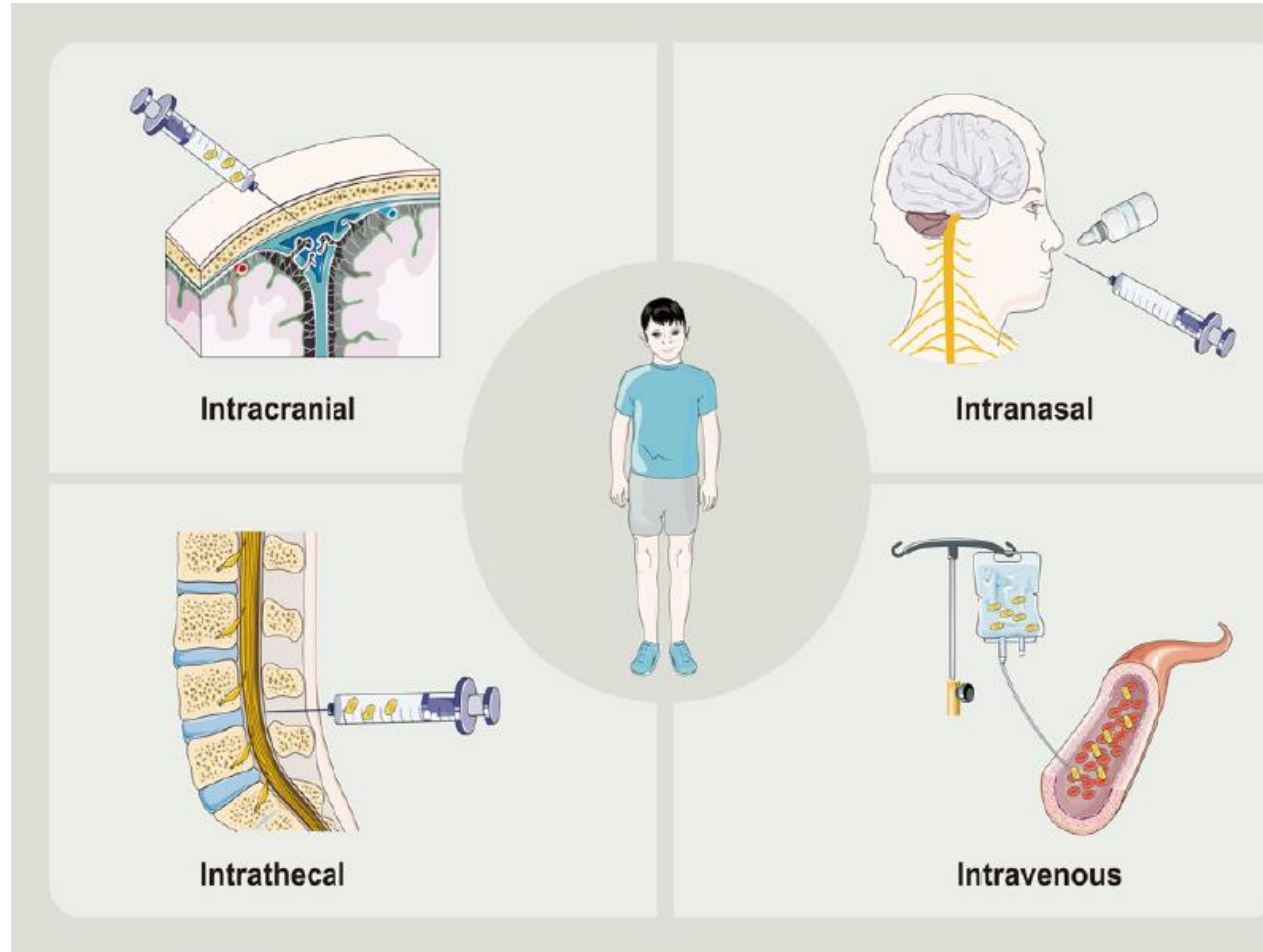
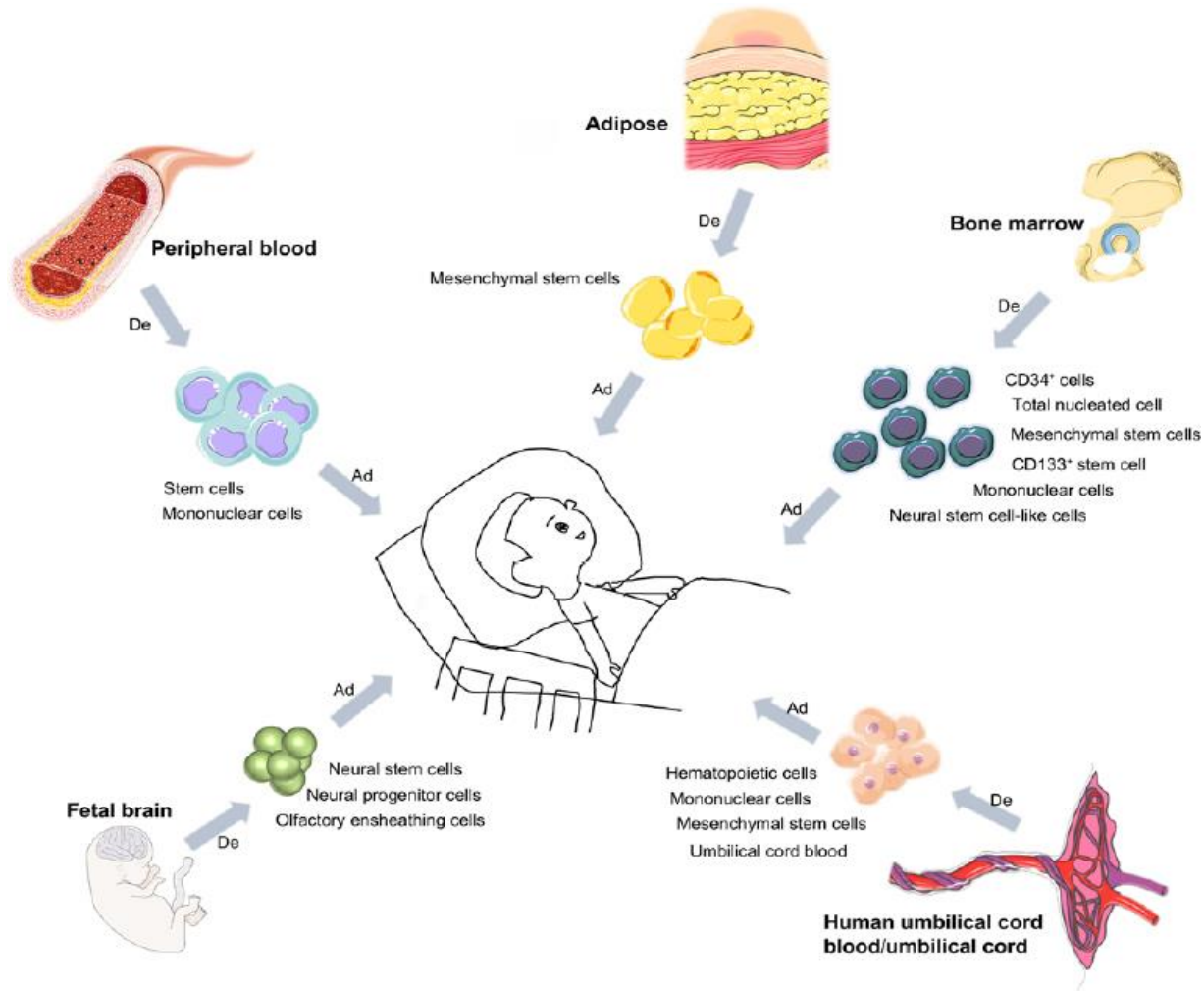


FIGURE 27-11 Postulated sites of spasmolytic action of tizanidine (α_2), benzodiazepines ($GABA_A$), and baclofen ($GABA_B$) in the spin. Tizanidine may also have a postsynaptic inhibitory effect. Dantrolene acts on the sarcoplasmic reticulum in skeletal muscle. Glu, glutamat neuron.

Baklofen (p-chlorophenyl-GABA) - aktivni GABA-mimetik; agonist GABA B Rec -> hiperpolarizacija; povečana prepustnost K^+ ; znižja spastičnost; manj sedacije; ne znižja miš. moči kot dantrolene.

Zarodne celice



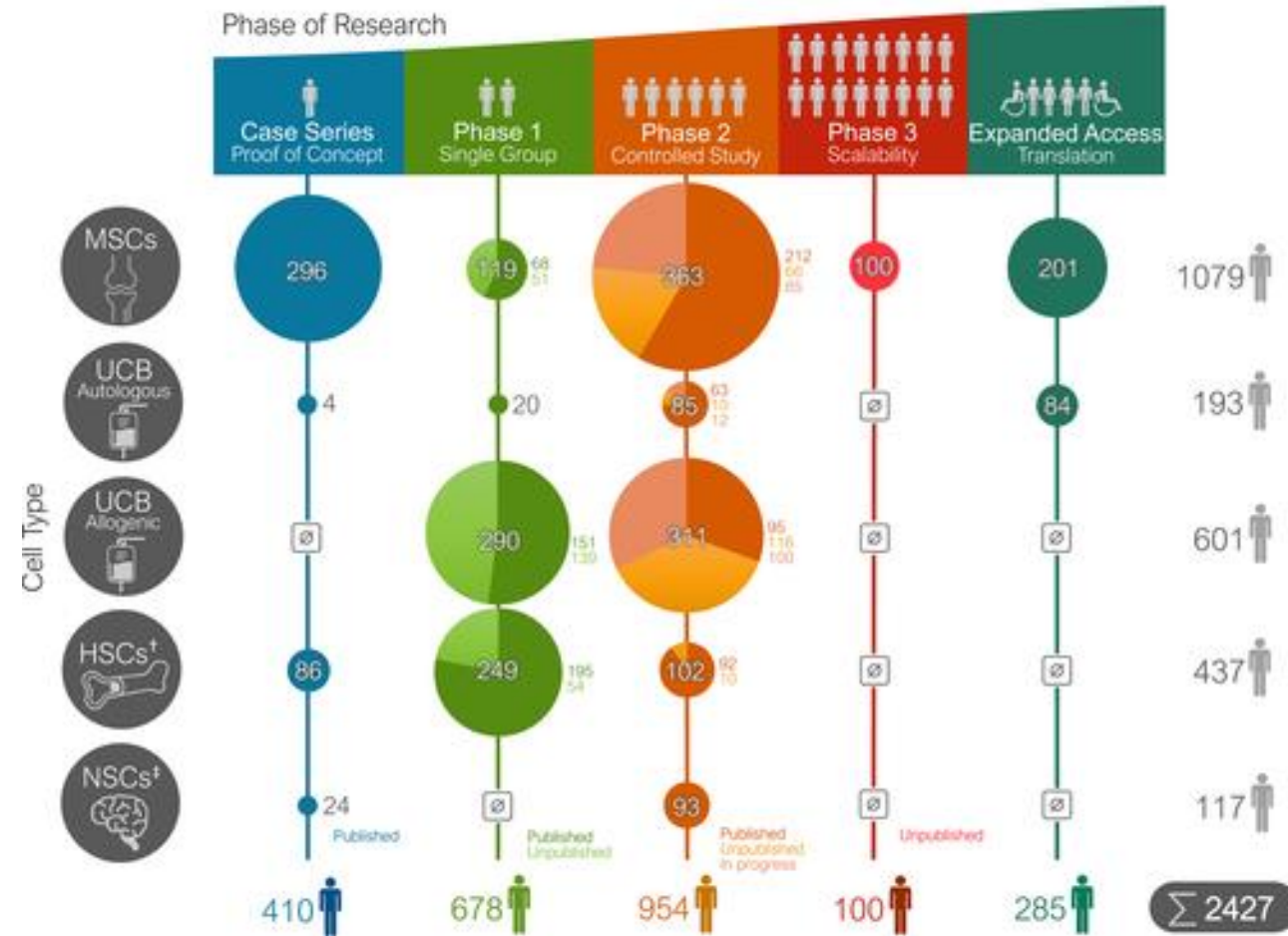
Progress in clinical trials of stem cell therapy for cerebral palsy. REVIEW; 2021, 16: 7; 1377-1382.

Zhong-Yue Lv ORC ID , Ying Li ORC ID , Jing Liu PhD ORC ID

Stem Cell Clinical Research Center, National Joint Engineering Laboratory, Regenerative Medicine Center, The First Affiliated Hospital of Dalian Medical University; Dalian Innovation Institute of Stem Cell and Precision Medicine, Dalian, Liaoning Province, China

Zarodne celice

- 15 let: 1. th. CP s celicami popkovnične krvi (Sun *et al.*)
- haematopoetske c, mezenhimske stromalne c, c. živčnega izvora, c. popkovnične krvi
- ni zaenkrat odobren:
- dokumentirani učinki vprašljivi, stroškovna učinkovitost slaba/ni
- Razvoj globalne trgovine z matičnimi celicami na privatnih klinikah – ali je bolnik postal potrošnik?



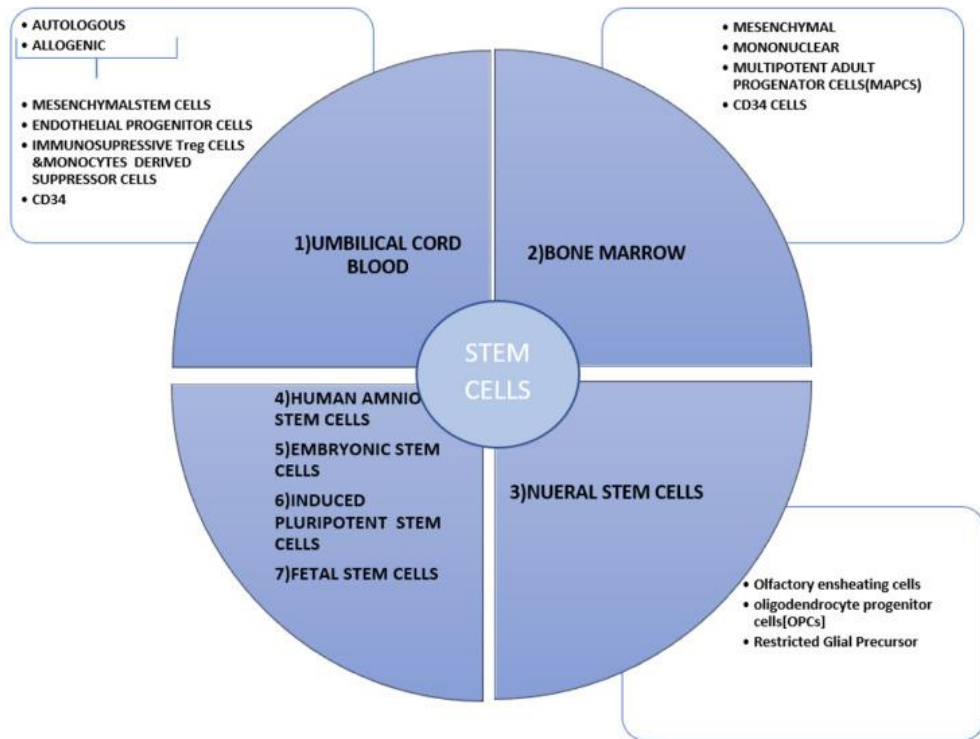
Novak I, Walker K, Hunt RW, Wallace EM, Fahey M, Badawi N. Concise review: Stem cells interventions for people with cerebral palsy: Systematic review with meta-analysis. *Stem Cells Transl. Med.* 2016; 5: 1014–25.

Eggenberger S, Boucard C, Schoeberlein A et al. Stem cell treatment and cerebral palsy: Systemic review and meta-analysis. *World J. Stem Cells* 2019; 11: 891–903.

Petersen A, Seear K, Munsie M. Therapeutic journeys: The hopeful travails of stem cell tourists. *Sociol. Health Illn.* 2014; 36: 670–85.

Novak I, Morgan C, Fahey M et al. State of the evidence traffic lights 2019: Systematic review of interventions for preventing and treating children with cerebral palsy. *Curr. Neurol. Neurosci. Rep.* 2020; 20: 3.

Zarodne celice



Delovanje: **NE nadomeščanje c. pač pa celična intervencija – ustvarjanje okolja:**

1. Regeneracija: nadomestilo ali/in popravilo poškodovanih c. v nove astrocite/mikroglijo (?)

2. **Protivnetno in imunomodulatorno** delovanje: zmanjša izločanje citotoksinov, prostih kisikovih radikalov -> zmanjša poškodbo beline Zveča sistemsko imunsko inhibicijo, izloča protivnetne + pro-vnetne citokine (TNF iz makrofagov) (Za HIE?)

3. **Trofično** delovanje: izločanje nevrotrofinov, ki spodbujajo endogeno c. migracijo, proliferacijo, protiapoptotsko delovanje, diferenciacijo, angiogenezo; parakrino delovanje v poškodovanih predelih

Intratekalno, intraspinalno, intracerebralno (možg. Transplantacija), intraventrikularno, i.v., i.a., i.m., intranazalno (za HIE?)

10 na 7 c./kg TT; vsaj dvakrat, maks. 24 mes, -> plj. Embolizmi

Ranljivi novorojenčki (pod 5 let), BBB – intracerebralno vs. Periferno -> ujetje v druge organe, pljučni embolizmi

Motorični deficit (ostalo ne) v ZDA (2006 to 2010):

GMFCS: Izboljšanje I (38% to 48%) & V (17% to 20%),

Poslabšanje II (16% to 8%) & III (13% to 9%),

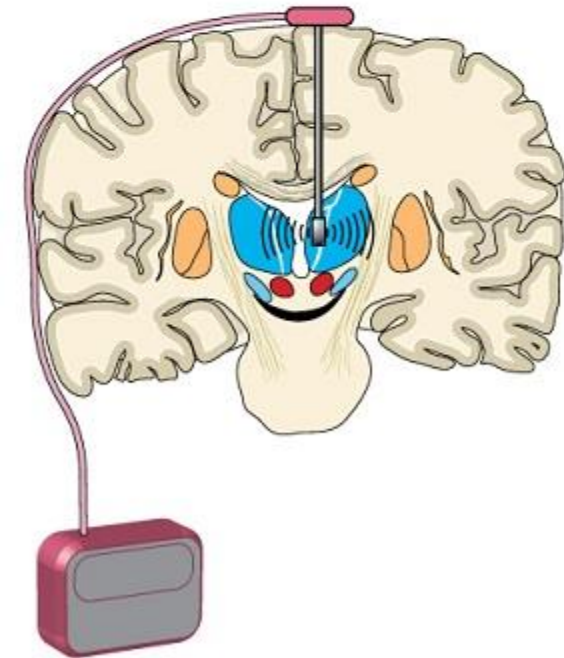
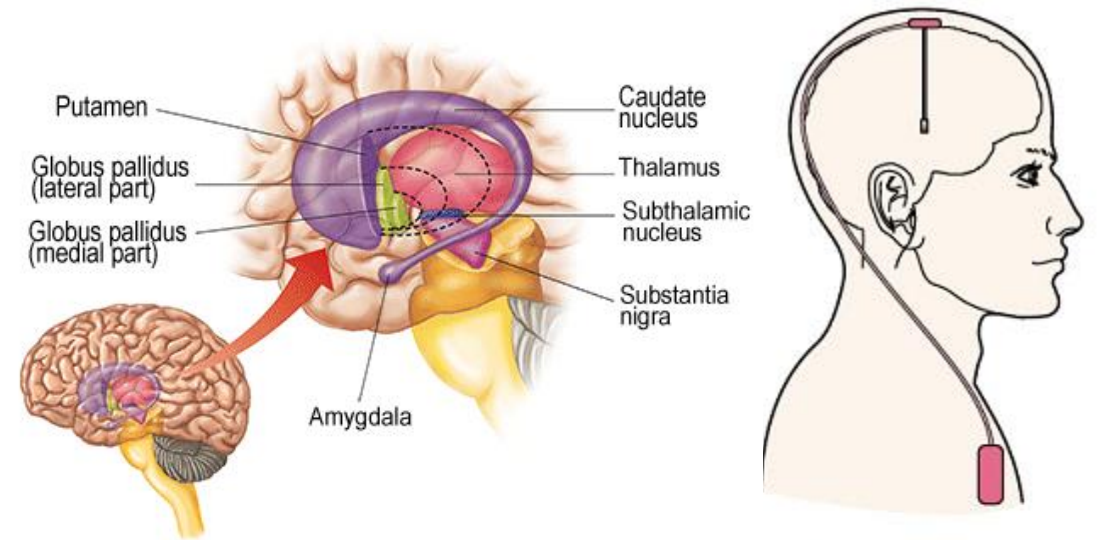
Isto IV

Po 6 mes izboljššan QoL

Nevromodulacija – „DBS“

- 40 let funkcionalne nevrokr
- Genetske DYS1 (+ 80-99%)
- Cervikalna dystonia (torticollis) (+40-60%)
- Tardivna dyskinesia (+ 80%) improvement is common
- CP (+ 0-20%)

- 1-3% tveganje za ICK (koma, smrt), 5% za okužbo
- Prilagajanje (nastavitve, mesto)



DBS

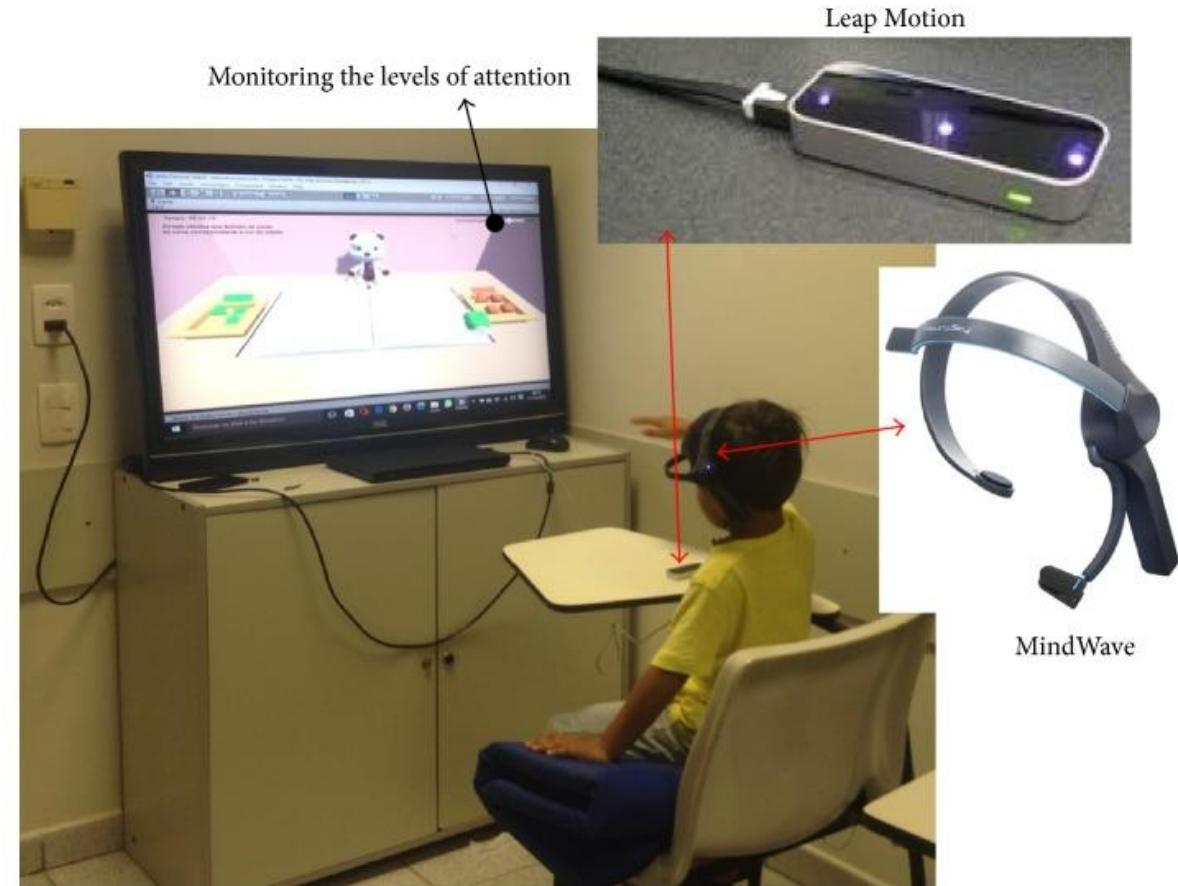
- NE pričakujemo izboljšanja šibkosti, spastičnosti, selektivne deficite motorike, ataksije, dispraksije ali senzorne in kongnitivne disfunkcije
- NE kompenzira za strukturne lezije, infomarcijske/procesne šibkosti
- **Kot nevromodulacija pa spremeni vzorce živčne aktivnosti**
- Zmanjša znake diskinetične CP – atetoze
- TOR1A/DYT1 gen
- Za mobilno distonijo (v mirovanju normo/hipotonus!)

Air EL, Ostrem JL, Sanger TD, Starr PA. Deep brain stimulation in children: experience and technical pearls. J Neurosurg Pediatr 2011; 8: 566– 74.

Sanger TD. Deep brain stimulation for cerebral palsy: where are we now? DMCN, 18 June 2019

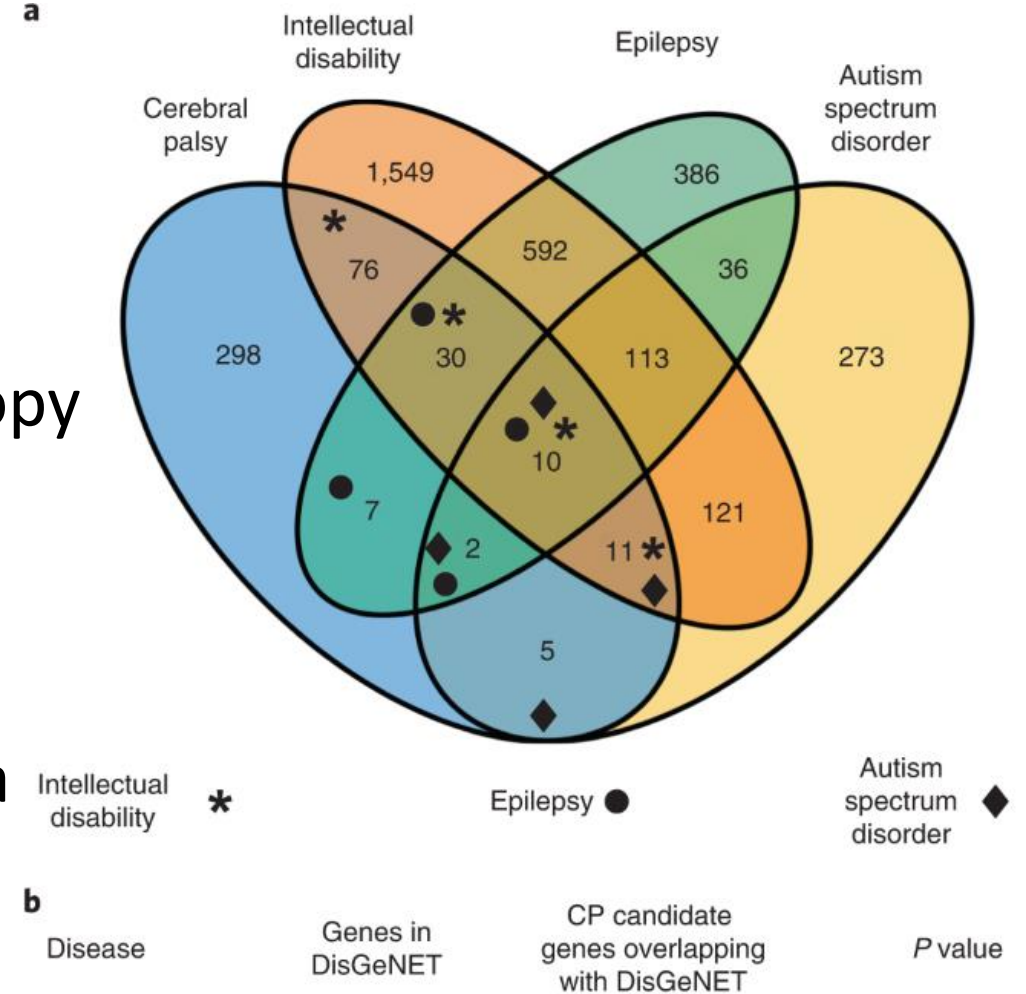
<https://doi.org/10.1111/dmcn.14295>

Kombinacije z virtualnim okoljem, EEG „Serious gaming“



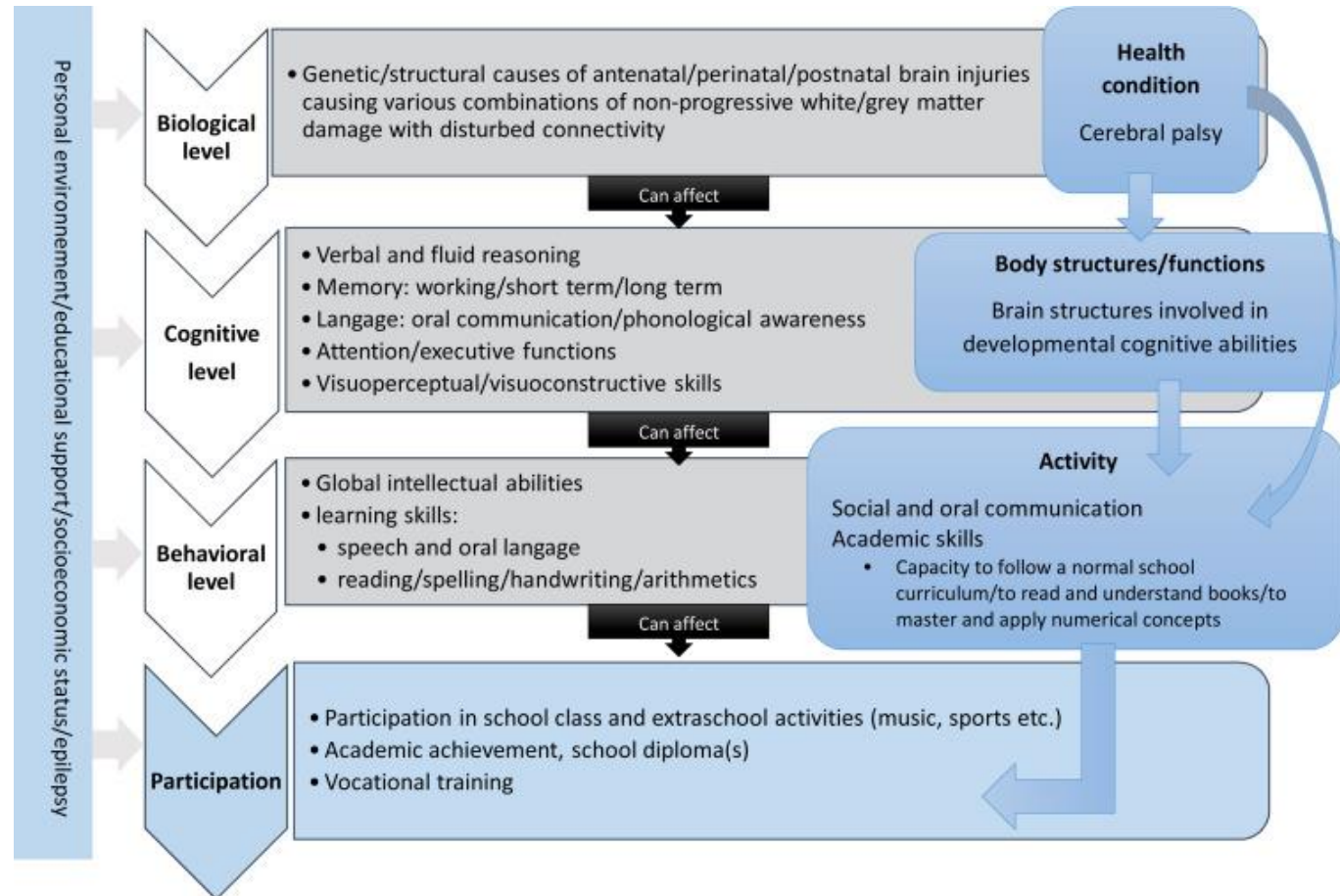
Genetika CP s potencialom zdravljenja?

- single nucleotide variants (SNVs) & genomic copy number variants (CNVs)
- PVL v pacientih z ATL1 in RHOB variantami
- Konektivnost: rast nevitov ekstracelularno v matriksu; celica-matrix interakcija, citoskeletna dinamika, Rho GTPaza, SCN8A, KCNMA1
- Epigenomika (metilacija)
- Transkriptomika (MAPK/PI3K/AKT – celično signaliziranje – povezanost nevitov)



Jin, S.C., Lewis, S.A., Bakhtiari, S. *et al.* Mutations disrupting neuritogenesis genes confer risk for cerebral palsy. *Nat Genet* **52**, 1046–1056 (2020).
<https://doi.org/10.1038/s41588-020-0695-1>

Ali otroke popravljamo?!



We do not heal the past
by dwelling there; we heal
the past by living fully in
the present.

– Marianne Williamson



Do not **dwell** in the **past**,
do not **dream** of the **future**,
concentrate the **mind**
on the **present moment**.

