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Interventions and Management

1. NeuroRehabilitation. 2014 Jan 28. [Epub ahead of print]

High doses of a new botulinum toxin type A (NT-201) in adult patients with severe spasticity following brain injury and cerebral palsy.

Intiso D1, Simone V2, Di Rienzo F1, Iarossi A1, Paziienza L1, Santamato A3, Maruzzi G1, Basciani M1.

BACKGROUND: Spasticity can be a severe disabling disorder requiring high-dose injections of botulinum toxin type A (BoNT-A). Efficacy and safety of high BoNT-A doses in reducing multi-level spasticity of subjects with brain injury and cerebral palsy were investigated. Pain and functional outcome were also assessed. **METHOD:** High doses (up to 840 IU) of incobotulinumtoxinA were injected in adult subjects with severe spasticity of the upper and lower limbs due to brain injury (BI) and cerebral palsy (CP). The Modified Ashworth Scale, Visual Analogue scale, Glasgow Outcome Scale, Franchay Arm Test (FAT) and Barthel Scale were employed to assess spasticity, pain and functional outcome at baseline, and 4 and 16 weeks after BoNT-A injection. **RESULTS:** Twenty-two (12 M, 10 F; mean age 38.1 ± 13.7 years) subjects - 16 subjects with BI and 6 with CP - were enrolled. Elbow, wrist, fingers and ankle muscles showed significant spasticity reduction after BoNT-A injections. The mean FAT score improved, but the benefit was not significant. Three (13.6%) subjects complained of mild adverse events. **CONCLUSION:** High-dose BoNT-A injections were effective and safe in reducing spasticity of BI and CP subjects. A significant reduction of the pain was also observed, but global functionality and arm dexterity were unchanged.

[PMID: 24473245](https://pubmed.ncbi.nlm.nih.gov/24473245/) [PubMed - as supplied by publisher]

2. Eur J Paediatr Neurol. 2014 Jan 8. pii: S1090-3798(14)00005-1. doi: 10.1016/j.ejpn.2013.12.010. [Epub ahead of print]

Evaluation of functional goal outcomes using the Canadian Occupational Performance Measure (COPM) following Deep Brain Stimulation (DBS) in childhood dystonia.

Gimeno H1, Tustin K2, Lumsden D3, Ashkan K4, Selway R4, Lin JP2.

PURPOSE: To evaluate the functional goal-directed outcomes of Deep Brain Stimulation (DBS) in childhood dystonia according to aetiology and to explore relationship with a traditional impairment-based measure. **METHOD:** This is a prospective case series study involving thirty children with dystonia with a 1-year follow-up post-DBS. The Canadian Occupational Performance Measure (COPM) and Burke-Fahn-Marsden Dystonia Rating

Scale (BFMDRS) were used as primary outcome measures. Results were analysed based on aetiology in 3 groups: 1. primary/primary plus dystonia; 2. secondary dystonia-cerebral palsy (CP); 3. secondary dystonia-non-CP group. Correlation between functional outcome using COPM and dystonia improvement as captured by BFMDRS was measured. RESULTS: All groups demonstrated significant improvement in individualised goal attainment, measured with the COPM, at 1-year post-DBS. The secondary dystonia-CP group also achieved significant improvement at 6 months for performance and satisfaction scores. In the majority of secondary dystonias, the BFMDRS failed to demonstrate significant improvement. A linear correlation between change in BFMDRS and COPM scores was observed when the entire cohort was analysed. INTERPRETATION/CONCLUSIONS: DBS improved functional performance, independently of the dystonic phenotype. Improvements in individualized COPM functional goal areas were seen in the absence of significant changes in BFMDRS scores, highlighting the relative insensitivity of impairment scales in this patient group.

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3. Res Dev Disabil. 2014 Jan 27. pii: S0891-4222(14)00013-4. doi: 10.1016/j.ridd.2014.01.009. [Epub ahead of print]

Reliability and validity of the Korean version of the Trunk Control Measurement Scale (TCMS-K) for children with cerebral palsy.

Jeon JY1, Shin WS2.

The Trunk Control Measurement Scale (TCMS) was developed by Lieve Heyrman in 2011 to evaluate the clinical features of impaired trunk control ability in patients with cerebral palsy (CP). This study aimed to demonstrate the reliability and validity of the Korean version of the Trunk Control Measurement Scale (TCMS-K) for children with CP. Fifty children with spastic CP (mean age 9.08±3.75) participated in the study. They were classified using the Gross Motor Function Classification System and the Manual Ability Classification System. The intraclass correlation coefficient (ICC) value of the inter-rater reliability for the TCMS-K was .987-.998, and the intra-rater reliability was .947-.996. The Spearman rank correlation coefficient between the TCMS-K and the Gross Motor Function Measure-B dimension was .860. The results of the study support that the TCMS-K has a high reliability and validity, which is similar to the original version. Thus, the TCMS-K is a suitable evaluation tool to assess the qualitative performance of trunk control and sitting balance for children with CP, and we expect that it will be a very useful tool for clinicians and researchers.

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4. Spine (Phila Pa 1976). 2014 Jan 29. [Epub ahead of print]

Morphological Characteristics of Cervical Spine in Patients With Athetoid Cerebral Palsy and the Accuracy of Pedicle Screw Placement.

Kato S, Shoda N, Chikuda H, Seichi A, Takeshita K.

STRUCTURED: Study Design. A retrospective study. Objective. To investigate the morphology of the cervical spine in patients with athetoid cerebral palsy (CP), and to evaluate its relationship with the breach of cervical pedicle screws. Summary of Background Data. Cervical pedicle screws have been increasingly used in surgery for patients with CP, but screw misplacement is not uncommon. Although the altered morphology of the cervical spine in patients with CP may result in this high breach rate, few studies have examined the cervical pedicle profile. Methods. We retrospectively analyzed 31 cervical myelopathy patients with CP, as well as 30 patients with cervical spondylotic myelopathy (CSM), who underwent posterior decompression surgery. The pedicle outer diameter, inner diameter, transverse angle and lateral mass deformity were investigated by obtaining preoperative computed tomography (CT) images. The accuracy of the placement of 56 pedicle screws used in fusion surgery for 12 CP patients was also analyzed using postoperative CT images. Results. The outer diameter of the pedicle in CP ranged from 3.3 to 9.6 mm, and was larger than that in CSM at all cervical levels except for C7. Pedicle sclerosis

was more frequently observed in CP than in CSM (23% vs. 7.3%, $P < 0.001$). The transverse angle at C3 and C4 was larger, and lateral mass deformity was more frequently observed in CP than in CSM. The critical breach of pedicle screws in CP was found in 29%. A multivariate analysis revealed that pedicle sclerosis was associated with an increased risk of breach (odds ratio: 6.3; 95% confidence interval: 1.03 - 39.0; $p = 0.047$). Conclusions. The pedicle diameter in patients with CP was relatively large, but pedicle sclerosis, a wide transverse angle and lateral mass deformity were frequently observed. Sclerotic pedicles were associated with a higher risk of critical breach.

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5. Neuropsychiatr Dis Treat. 2014 Jan 23;10:111-122. eCollection 2014.

Epidemiological, humanistic, and economic burden of illness of lower limb spasticity in adults: a systematic review.

Martin A1, Abogunrin S1, Kurth H2, Dinet J2.

BACKGROUND: The purpose of this study was to investigate the epidemiological, humanistic, and economic burden of illness associated with adult lower limb spasticity (LLS) and its complications. **METHODS:** A systematic search of MEDLINE and EMBASE identified 23 studies published between January 2002 and October 2012 that assessed the epidemiology, impact, and resource use associated with LLS. A hand-search of four neurology conferences identified abstracts published between 2010 and 2012. **RESULTS:** LLS was found to occur in one third of adults after stroke, half to two thirds with multiple sclerosis, and three quarters with cerebral palsy. LLS limits mobility and reduces quality of life. No clear association was found between LLS and occurrence of pain, development of contractures, or risk of falls. **CONCLUSION:** The evidence on the burden of LLS and its complications is surprisingly limited given the condition's high prevalence among adults with common disorders, such as stroke. Further research is needed to clarify the impact of LLS, including the likelihood of thrombosis in spastic lower limbs. The dearth of high-quality evidence for LLS suggests a lack of awareness of, and interest in, the problem, and therefore, the unmet need among patients and their carers.

[PMID: 24482572](#) [PubMed - as supplied by publisher] Free PMC Article

6. Nature. 2014 Jan 2;505(7481):108-11. doi: 10.1038/nature12732. Epub 2013 Nov 17.

Structural basis for recognition of synaptic vesicle protein 2C by botulinum neurotoxin A.

Benoit RM1, Frey D2, Hilbert M2, Kevenaar JT3, Wieser MM1, Stirnimann CU4, McMillan D5, Ceska T5, Lebon F6, Jaussi R1, Steinmetz MO1, Schertler GF7, Hoogenraad CC8, Capitani G1, Kammerer RA1.

Botulinum neurotoxin A (BoNT/A) belongs to the most dangerous class of bioweapons. Despite this, BoNT/A is used to treat a wide range of common medical conditions such as migraines and a variety of ocular motility and movement disorders. BoNT/A is probably best known for its use as an antiwrinkle agent in cosmetic applications (including Botox and Dysport). BoNT/A application causes long-lasting flaccid paralysis of muscles through inhibiting the release of the neurotransmitter acetylcholine by cleaving synaptosomal-associated protein 25 (SNAP-25) within presynaptic nerve terminals. Two types of BoNT/A receptor have been identified, both of which are required for BoNT/A toxicity and are therefore likely to cooperate with each other: gangliosides and members of the synaptic vesicle glycoprotein 2 (SV2) family, which are putative transporter proteins that are predicted to have 12 transmembrane domains, associate with the receptor-binding domain of the toxin. Recently, fibroblast growth factor receptor 3 (FGFR3) has also been reported to be a potential BoNT/A receptor. In SV2 proteins, the BoNT/A-binding site has been mapped to the luminal domain, but the molecular details of the interaction between BoNT/A and SV2 are unknown. Here we determined the high-resolution crystal structure of the BoNT/A receptor-binding domain (BoNT/A-RBD) in complex with the SV2C luminal domain (SV2C-LD). SV2C-LD consists of a right-handed, quadrilateral β -helix that associates with BoNT/A-RBD mainly through backbone-to-backbone interactions at open β -strand edges, in a manner that resembles the inter-strand interactions in amyloid structures. Competition experiments identified a peptide that inhibits the formation of the complex. Our findings provide a strong platform for the development of novel antitoxin agents and for the rational design of BoNT/A variants with improved therapeutic properties.

[PMID: 24240280](#) [PubMed - indexed for MEDLINE]

7. Zhongguo Dang Dai Er Ke Za Zhi. 2014 Jan;16(1):35-9.**Early multi-disciplinary intervention reduces neurological disability in premature infants [Article in Chinese]**

Chen GF, Zhang YF, Chen MQ, Wang XL, Long Q, Kong Q, Mao H.

OBJECTIVE: This study aimed to evaluate the effectiveness of multi-disciplinary treatment approaches in reducing neurological disabilities in premature infants. **METHODS:** A total of 117 infants who were born premature in our hospital between March 2008 and February 2010 but had no congenital malformations and no severe neonatal complications, were enrolled in this study. They were randomly allocated to a multi-disciplinary treatment group (n=63) and a control group (n=54). While patients in the control group underwent an early conventional treatment, those in the multi-disciplinary treatment group were subjected to regular development monitoring, neurological examination and screening for brain injury, neuro-nutrition and neurodevelopment therapies, and rehabilitation training. **RESULTS:** The incidence rates of abnormalities in posture, reflex, sleep, muscle tone and EEG were significantly lower in the multi-disciplinary treatment group than in the control group ($P<0.05$) at corrected postnatal ages of 6-12 months. At corrected postnatal ages of 6, 12, 18 and 24 months, both mental development index (MDI) and psychomotor development index (PDI) scores were significantly higher in the multi-disciplinary treatment group than in the control group ($P<0.05$). At corrected postnatal age of 3 years, incidence rates of cerebral palsy, language barrier, abnormal muscle tone and hearing impairment were significantly lower in the multi-disciplinary treatment group than in the control group ($P<0.05$). **CONCLUSIONS:** Early multi-disciplinary intervention approaches may significantly improve mental and motor developments and reduce the incidence of cerebral palsy-associated neurological disabilities in premature infants.

[PMID: 24461175](#) [PubMed - in process] Free full text

8. Pediatr Neurol. 2013 Dec 5. pii: S0887-8994(13)00714-5. doi: 10.1016/j.pediatrneurol.2013.11.022. [Epub ahead of print]**Spectrum of Visual Disorders in a Population-Based Cerebral Palsy Cohort.**

Dufresne D1, Dagenais L1, Shevell MI2; REPACQ Consortium.

BACKGROUND: Children with cerebral palsy are known to be at increased risk for visual impairment. **METHODS:** In a population-based sample drawn from a geographically defined registry, the profile of visual impairment in children with cerebral palsy was investigated. **RESULTS:** Close to half (49.8%; 106/213) had a visual impairment. The majority of these had strabismus (55.7%; 59/106) and a slightly lesser fraction had refractive errors (20.7%; 22/106) or severe visual loss (18.9%; 20/106). The vast majority of children with severe visual loss were spastic quadriplegic (83%; 17/20) or nonambulatory (i.e., Gross Motor Function Classification Scale IV/V, 80%; 16/20). **CONCLUSIONS:** Knowledge of this profile will assist practitioners heightening their appreciation of potential visual disturbances in certain subsets of cerebral palsy.

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9. Int J Speech Lang Pathol. 2014 Jan 29. [Epub ahead of print]**Impact of sentence length and phonetic complexity on intelligibility of 5-year-old children with cerebral palsy.**

Allison KM, Hustad KC.

Reduced speech intelligibility is a barrier to effective communication for many children with cerebral palsy (CP). Many variables may impact intelligibility, yet little research attention has sought to quantify these variables. This study examined the influence of sentence characteristics on intelligibility in two groups of children with CP (those with and without dysarthria) and typically-developing children. Questions addressed effects of sentence length on transcription intelligibility among groups; effects of phonetic complexity on intelligibility; and differences in the

relationship between sentence characteristics and intelligibility across individual children with dysarthria. Speech samples varying in length from 2-7 words were elicited from 16 children with CP (mean age 59.6 months) and eight typically-developing children (mean age = 59.8 months). One hundred and nineteen naïve listeners made orthographic transcriptions of the children's sentence productions. Sentence length and phonetic complexity affected intelligibility for all groups of children, but had a greater impact on intelligibility for children with dysarthria than those without speech motor impairment. Variable relationships between sentence characteristics and intelligibility were found across individual children with dysarthria. Results suggest that reducing both the length and phonetic complexity of utterances may enhance intelligibility for children with dysarthria. However, there may be important individual differences in the impact of one or both types of sentence characteristics. This highlights the importance of considering individual speech motor profiles when deciding on treatment strategies.

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10. Disabil Rehabil. 2014 Jan 28. [Epub ahead of print]

Child engagement in daily life: a measure of participation for young children with cerebral palsy.

Chiarello LA, Palisano RJ, McCoy SW, Bartlett DJ, Wood A, Chang HJ, Kang LJ, Avery L.

Purpose: The objectives of this study were to determine the: (1) internal consistency and test-retest reliability of the Child Engagement in Daily Life measure; (2) construct validity of the measure (known groups methods), that is, the ability of the measure to discriminate participation in family and recreational activities and self-care among young children of varying age and motor ability and between children with and without cerebral palsy, and (3) stability and hierarchical ordering of the items for young children with CP to devise an interval-level scoring system. Methods: 429 children with CP and their parents and 110 parents of children without CP participated in this methodological study. Parents completed the Child Engagement in Daily Life measure and therapists assessed the children's gross motor function. Rasch analysis was used to create an interval-level measure. Results: Children's frequency in and enjoyment of participation in family and recreational activities and self-care varied by age and gross motor ability. Internal consistency of the domains of the measure was high, Cronbach alpha values ranging from 0.86 to 0.91; test-retest for participation in family and recreational activities was acceptable, ICC=0.70, and in self-care was high, ICC=0.96. The items in the measure had a good fit and a logical hierarchical ordering. Conclusion: Study results support the validity and reliability of the Child Engagement in Daily Life measure as an assessment of participation in family and recreational activities and self-care for young children with CP. Implications for Rehabilitation Participation in family and recreational activities and self-care for young children with cerebral palsy can be reliably and validly assessed using the Child Engagement in Daily Life measure. Service providers are encouraged to support young children's participation in family and recreational activities and self-care.

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Prevention and Cure

11. Cell Transplant. 2014 Jan 29. [Epub ahead of print]

Mannitol-enhanced delivery of stem cells and their growth factors across the blood brain barrier.

Gonzales-Portillo GS, Sanberg PR, Franzblau M, Gonzales-Portillo C, Diamandis T, Staples M, Sanberg CD, Borlongan CV.

Ischemic brain injury in adults and neonates is a significant clinical problem with limited therapeutic interventions. Currently, clinicians have only tPA available for stroke treatment, and hypothermia for cerebral palsy. Due to the lack of treatment options, there is a need for novel treatments such as stem cell therapy. Various stem cells including cells from embryo, fetus, perinatal, and adult tissues have proved effective in preclinical and small clinical trials. However, a limiting factor in the success of these treatments is the delivery of the cells and their by-products (neurotrophic factors) into the injured brain. We have demonstrated that mannitol, a drug with the potential to transiently open the blood brain barrier and facilitate the entry of stem cells and trophic factors, is a possible solution to the delivery problem. The combination of stem cell therapy and mannitol may improve therapeutic

outcomes in adult stroke and neonatal cerebral palsy.

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12. Early Hum Dev. 2014 Jan 22. pii: S0378-3782(13)00329-0. doi: 10.1016/j.earlhumdev.2013.12.010. [Epub ahead of print]

The impact of cesarean section on neonatal outcome of infants born at 23 weeks of gestation.

Furukawa S1, Sameshima H2, Ikenoue T2.

OBJECTIVE: Determine the impact of cesarean section (CS) on neonatal outcome of infants born at 23 weeks of gestation. **METHODS:** A retrospective study was performed involving 34 infants born at 23 weeks and 91 infants born at 24-26 weeks. Indications necessitating delivery were severe pregnancy induced hypertension, non-reassuring fetal heart rate patterns (NRFHRs), or intrauterine infection (IUI). Obstetrical indication for CS included NRFHR and breech presentation. Poor outcome included neonatal death or cerebral palsy. Univariate and multiple logistic analyses were performed to determine the effect of CS for obstetrical indications on poor outcome. **RESULTS:** The incidence of poor outcome was significantly higher at 23 weeks (number of poor outcomes/total number: 22/34) compared to that (31/91) at 24-26 weeks ($p < 0.01$). The incidence of a poor outcome was significantly higher at 23 weeks for infants having NRFHR (11/16) compared to those at 24-26 weeks (15/43, $p = 0.02$). However, the incidence of a poor outcome was similar in infants with IUI (6/10 at 23 weeks versus 5/11 at 24-26 weeks, $p = 0.41$). Vaginal birth in cases of obstetrical indication for CS at 23 weeks was associated with higher risk of a poor outcome (odds ratio: 8.2). In contrast, the risk at 24-26 weeks was not higher (OR, 0.8). After adjustment using variables of vaginal birth and IUI, vaginal birth significantly affected poor outcome (OR, 13.0). **CONCLUSION:** Poor neonatal outcome was closely related to the mode of delivery, suggesting that CS for obstetrical indication at 23 weeks may improve neonatal outcome.

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13. Exp Neurol. 2013 Dec;250:282-92. doi: 10.1016/j.expneurol.2013.10.003. Epub 2013 Oct 9.

Partial neuroprotection by nNOS inhibition during profound asphyxia in preterm fetal sheep.

Drury PP, Davidson JO, van den Heuvel LG, Tan S, Silverman RB, Ji H, Blood AB, Fraser M, Bennet L, Gunn AJ.

Preterm brain injury is partly associated with hypoxia-ischemia starting before birth. Excessive nitric oxide production during HI may cause nitrosative stress, leading to cell membrane and mitochondrial damage. We therefore tested the hypothesis that therapy with a new, selective neuronal nitric oxide synthase (nNOS) inhibitor, JI-10 (0.022mg/kg bolus, $n = 8$), given 30min before 25min of complete umbilical cord occlusion was protective in preterm fetal sheep at 101-104day gestation (term is 147days), compared to saline ($n = 8$). JI-10 had no effect on fetal blood pressure, heart rate, carotid and femoral blood flow, total EEG power, nuchal activity, temperature or intracerebral oxygenation on near-infrared spectroscopy during or after occlusion. JI-10 was associated with later onset of post-asphyxial seizures compared with saline ($p < 0.05$), and attenuation of the subsequent progressive loss of cytochrome oxidase ($p < 0.05$). After 7days recovery, JI-10 was associated with improved neuronal survival in the caudate nucleus ($p < 0.05$), but not the putamen or hippocampus, and more CNPase positive oligodendrocytes in the periventricular white matter ($p < 0.05$). In conclusion, prophylactic nNOS inhibition before profound asphyxia was associated with delayed onset of seizures, slower decline of cytochrome oxidase and partial white and gray matter protection, consistent with protection of mitochondrial function.

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