Spasticity in children and young people with non-progressive brain disorders: management of spasticity, co-existing motor disorders and their early musculoskeletal complications

Oral drugs

Bibliographic details	Number of Participant Participant Characteristics	Intervention characteristics	Outcome measures and results	Quality assessment	Reviewer comment
Authors Scheinberg,A., Hall,K., Lam,L.T., O'Flaherty,S. **Year of publication** 2006 **Study location** Australia **Ref ID** 56461 **Type of study** Randomised controlled study **Aim of study** To assess: -the effectiveness of baclofen in reducing spasticity and improving passive function in children with cerebral palsy (CP) and	**Inclusion Criteria** Convenience sample drawn from a physical disability clinic at a tertiary paediatric hospital Age: 1 to 15 years CP and clinically significant spasticity defined as: increased tone or spasms, causing pain, reported difficulty with cares or impaired movement Children with dystonia as additional motor disorder also included **Exclusion Criteria** Children already taking oral anti-spasticity medication Epileptic seizure within the previous month **Baseline characteristics** **Intervention Group**	**Intervention** Group A: 13 weeks of oral baclofen followed by a 2-week non-treatment (washout) period and then 13 weeks of oral placebo Dose: -children aged < 8 years at enrolment: starting with 2.5 mg daily, increased weekly over a 7-week period to 10 mg three times a day and then continued at that dose for the next 5 weeks -children aged 8 or >8 years at enrolment: starting with 5 mg daily, increased weekly over a 9-week period to 20 mg three times a day and then continued at that dose for the next 3 weeks At the end of each 12-week period the drug (either baclofen or placebo) was tapered over 6 days **Comparison 1**	**Outcome 1** Modified Tardieu scores (MTS) score (mean, 95% CI) baseline: 20.9 (15.7 to 26.2) placebo: 27.1 (21.0 to 33.3) baclofen: 25.6 (19.4 to 25.8) change: -4.4 (-10.8 to 2.0) -Significance of different effects treatment: F (1,10)=0.9 ; p=0.36 period: F (1,10)=0.0 ; p=0.96 carry-over: F (1,10)=0.1 ; p=0.72 **Outcome 2** Goal Attainment Scaling (GAS) T score (mean, 95% CI) baseline: 35.0 placebo: 44.7 (39.3 to 50.0) baclofen: 51.3 (47.4 to 55.1) change: 6.6 (1.0 to 12.3) -Significance of different effects treatment: F (1,13)=4.5 ; p=0.05 period: F (1,13)=1.0 ; p=0.34 carry-over: F (1,13)=0.3 ; p=0.57 **Outcome 3** Paediatric Evaluation of Disability Inventory (PEDI) (mean, 95% CI)	Limitations Allocation concealment : unclear. but carried out by the hospital pharmacy Participants blinded to intervention : yes Carers blinded to intervention : yes Investigators blinded to intervention : yes Number of participants not completing treatment : none Number of participants with no available outcome data : none Selective outcome reporting : none Any other limitations : small sample size Indirectness Population : None Intervention : None	**Funding** The Children's Hospital at Wetsmead Small Grants Scheme **Other information** The same researcher explained study procedures to all children and carers, recorded demographic data, administered the parent questionnaire and assisted with measurements of MTS. An experienced paediatric physiotherapist undertook all other assessments including the MTS, GAS and PEDI. Assessments were performed at baseline and at the end of each 12-week period,

clinically significant spasticity -parent/carer reported side effects and whether they would choose the drug to be continued	(this is the total sample) 15 children -age range: 4 to 12 (mean: 7.4 years) -type of CP (n children): Spastic quadriplegia: 11 Spastic/dystonic quadriplegia: 4 GMFC IV: 10 GMFC V: 5 Mean weight: 17.2 kg (4.3) Intervention group: Group A (n=8) Comparison group: Group B (n=7) Specific sociodemographic and clinical characteristics other than study outcomes not reported separately for each group Baseline clinical outcomes not compared between groups -	Group B: 13 weeks of oral placebo followed by a 2-week non-treatment (washout) period and then 13 weeks of oral baclofen	a. Self care baseline: 15.2 (6.5 to 23.8) placebo: 20.5 (9.8 to 31.3) baclofen: 19.1 (8.8 to 29.4) change:-1.5 (-3.5 to 0.6) -Significance of different effects treatment: F (1,13)=1.7 ; p=0.21 period: F (1,13)=1.7 ; p=0.21 carry-over: F (1,13)=0.1 ; p=0.78 b. Mobility baseline: 17.5 (7.3 to 27.8) placebo: 18.7 (8.1 to 29.4) baclofen: 17.3 (6.9 to 27.7) change: -1.5 (-3.1 to 0.2) -Significance of different effects treatment: F (1,13)=3.6 ; p=0.08 period: F (1,13)=2.4 ; p=0.14 carry-over: F (1,13)=0.6 ; p=0.45 c. Social function baseline: 31.8 (18.0 to 45.6) placebo: 32.9 (19.3 to 46.5) baclofen: 32.7 (19.8 to 45.6) change: -0.2 (-3.0 to 2.6) -Significance of different effects treatment: F (1,13)=0.0 ; p=0.96 period:F (1,13)=1.4 ; p=0.27 carry-over: F (1,13)=0.0 ; p=0.95 Outcome 4 Parental satisfaction with the medication effect Placebo treatment 4 parents would continue with placebo 10 parents would not continue with placebo	Comparison : None Outcomes assessed : None	prior to tapering of the drug Both groups were followed up for an equal length of time Study had an appropriate length of follow up (GDG confirmed) and a precise definition of outcome A valid and reliable method was used to determine outcome The comparison groups recived the same care apart from the interventions studied **Selective outcome reporting** - **Sample size** This was a pilot study The sample size estimation was based on a single measure of the GAS, as according to authors there is a lack of quantifiable information in the literature of the assessments measures used in this study. It was assumed that baclofen had a large

			Baclofen treatment 6 parents would continue with baclofen 8 parents would discontinue baclofen treatment 1 parent was unsure. Outcome 5 Positive effects reported by parents during treatment periods Placebo treatment better sleeping (2), being more vocal (1), being more relaxed/settled (3) and less drooling were reported. Baclofen treatment period better sleeping (3), being more vocal (1), being easier to dress (1) and fewer spasms (1) were reported		treatment effect of 0.8 standard deviations when compared with placebo using a simple pair-comparison scenario. it was further assumed that there was negiglible carry-over as well as time period effects that potentially impacted on the analyisis of a cross-over study. A sample size of 14 would be sufficient to provide the study with 80% power to detect a tru difference, should one exist, using a significance level of 5%.

Bibliographic details	Number of Participant Participant Characteristics	Intervention characteristics	Outcome measures and results	Quality assessment	Reviewer comment
Authors Milla,P.J., Jackson,A.D. **Year of publication** 1977 **Study location** UK **Ref ID** 56476 **Type of study** Randomised controlled study **Aim of study** To assess the effects of baclofen in comparison with placebo on the disability due to pyramidal spasticity in children suffering from cerebral palsy (CP)	**Inclusion Criteria** Children aged 2 to 16 years, suffering from spasticity due to CP **Exclusion Criteria** Epilepsy, muscle hypotonia, severe psychiatric disturbance, renal or hepatic insufficiency, being treated with tricyclic or phenothiazine psychotropic drugs **Baseline characteristics** (total sample) 20 children attending either a hospital treatment centre as outpatients or local special shools for the physically handicapped -age range: 2 to 16 years -9 boys, 11 girls -type of CP (n children): Diplegic: 5 Hemiplegic: 7 Quadriplegic: 8 3 also exhibited athetosis -Ashworth scale (n children):	**Intervention** Oral baclofen 4-week treatment (inmediately followed by 4-week placebo treatment) First 2 weeks for dose adjustment in order to find optimal therapeutic level for each patient. This dose was then continued for the remaining 2 weeks. Initial dose: 10 mg daily in divided doses, increased in 3 increments over a period of 9 days, to maximun daily dosage of 60 mg (children over the age of 8 years) or 30 to 40 mg (children 2 to 7 years) Patients' routine physiotherapy continued unchanged throughout trial **Comparison 1** Placebo 4-week treatment (inmediately followed by 4-week baclofen treatment) First 2 weeks for dose adjustment in order to find optimal therapeutic level for each patient. This dose was then continued for the remaining 2 weeks. Initial dose: 10 mg daily in divided doses, increased in 3 increments over a period of 9 days, to maximun daily dosage of 60 mg (children over the age of 8 years) or 30 to 40 mg (children 2 to 7	**Outcome 1** Severity of spasticity (Ashworth Scale) after 28 days treatment (n of children) a. no increase in tone baclofen: 2 placebo: 0 b. slight increase in tone baclofen: 9 placebo: 3 c. more marked increase in tone baclofen: 8 placebo: 9 d. considerable increase in tone baclofen: 1 placebo: 8 e. affected parts rigid baclofen: 0 placebo: 0 14 children showed improvement whilst taking baclofen, whereas only 2 improved on placebo. 5/14 children who improved on baclofen did so by more than one category in the Ashworth Scale. The 2 children who improved on placebo did so by only one category 1/3 children with athetosis showed improvement whilst taking 60 mg/day and no improvement whilst receiving placebo Analysis of results by age groups did not show any statistically significant difference between younger (2 to 7 year olds) and older patients (7 to 16 year olds) **Outcome 2** Other clinical evaluation a. Extrapyramidal signs: recorded but not reported b. Cerebellar symptoms: no patients exhibited them c. Clonus: no patients exhibited it	Limitations Allocation concealment : unclear, but "random allocation" stated Participants blinded to intervention : yes Carers blinded to intervention : yes Investigators blinded to intervention : yes Number of participants not completing treatment : none Number of participants with no available outcome data : none Selective outcome reporting : unclear Any other limitations : none Indirectness Population : None Intervention : None Comparison : None Outcomes assessed : None	**Funding** Supplies of baclofen made available by CIBA Laboratories, Horsham, West Sussex. Other details unclear. **Other information** Patients assessed at the start of trial and subsequently at intervals of 7 days during the trial period by the same physician at the same time of the day. At the end of each treatment period the clinician, physiotherapist and the parent or nurse made independent overall evaluations of the patients' progress Both groups were followed up for an equal length of time Study did not have an appropriate length of follow-up or a precise definition of outcome. Unclear whether a valid and reliable method was used to determine outcome Unclear whether

	No increase in tone: 0 Slight increase in tone: 2 More marked increase in tone: 9 Considerable increase in tone: 9 Affected parts rigid: 0 **Intervention Group** -	years) Patients' routine physiotherapy continued unchanged throughout trial	d. Tendon reflexes: changes reported as "insignificant" **Outcome 3** Disabilities due to spasticity a. walking ability b. scissoring c. impairment of passive an active limb movements d.degree of self help e. manual dexterity These outcomes were only reported for the period when children were taking baclofen but not for placebo, therefore they are non-comparative and not included		investigators were kept blind to participants' exposure to the intervention or to other important confounding and prognostic factors **Selective outcome reporting** - **Sample size** No calculation reported

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Authors Mathew,A., Mathew,M.C., Thomas,M., Antonisamy,B 2005a. **Year of publication** 2005 **Study location** India **Ref ID** 56486 **Type of study** Randomised controlled study **Aim of study** To compare the effects of two dose sizes of diazepam and placebo given in a single bedtime dose	**Inclusion Criteria** All children with spastic CP below 12 years of age and weighting 15kg or less including those with co-morbid factors such as dysmorphic features or visual or hearing impairments. **Exclusion Criteria** Children who were in distress due to painful spasms were given diazepam and excluded. Children needing immediate medical attention due to acute illness were also excluded Children with hyptonic or extrapyramidal CP **Baseline characteristics** There were no significant differences among the three treatment groups (Total N = 180) for : Age up to 5 years Half dose diazepam group = 52/60 Full dose diazepam group = 57/60 Placebo group = 54/60 Sex (no of girls)	**Intervention** Sachets of diazepam prepared by the pharmacy (to be taken in a half or full dose) **Comparison 1** Sachets of placebo prepared by the pharmacy	**Outcome 1** 1) Mean change in muscle relaxation (modified Ashworth scale) Half dose diazepam group = 8.53 Full dose diazepam group = 13.32 Placebo group = 0.53 p<0.001 2) Adverse effects : Drowsiness No daytime drowsiness was reported for any child **Outcome 2** - **Outcome 3** -	Limitations Allocation concealment : computer generated in pharmacy Participants blinded to intervention : yes Carers blinded to intervention : yes Investigators blinded to intervention : yes Number of participants not completing treatment : 7/180 Number of participants with no available outcome data : 7/180 Selective outcome reporting : study powered for range of movement outcomes although mean change in muscle relaxation also reported. Outcomes for the well being of the child found in the full dose and placebo groups are reported in a separate publication above Any other limitations : standard deviations	**Funding** not stated **Other information** Informed consent: Yes Ethical approval :Research and Ethics committee of the Christian Medical College Hospital. Vellore Sample size calculation: based on clinical use of the drug over 6 months prior to trial. A total of 180 children (n=60 in each group) with 90% power (beta = 10%) and a two-tailed 2% significance level (alpha = 2%) would be required to detect a 10 degree change in the angle of flextion at ankle between the placebo and diazepam groups **Selective outcome reporting** - **Sample size** -

	Half dose diazepam group = 38/60 Full dose diazepam group = 36/60 Placebo group = 37/60 Socioeconomic status (High/Upper /Middle/Low) Half dose diazepam group = 3/6/14/37 Full dose diazepam group = 2/12/16/30 Placebo group = 5/9/18/28 Type of cerebral palsy (diplegia, hemiplegia, triplegia, double hemiplegia, quadriplegia) Half dose diazepam group = 15/10/3/2/30 Full dose diazepam group = 17/8/5/0/30 Placebo group = 7/8/4/5/36 Weight <5kgs Half dose diazepam group = 4/60 Full dose diazepam group = 4/60 Placebo group = 7/60 Height (51 to 70cm/71 to 90cm/91 to 110cm/110-130cm) Half dose diazepam			are not given Indirectness Population : none Intervention : none Comparison : none Outcomes assessed : none	

	group = 19/27/10/4 Full dose diazepam group = 26/29/5/0 Placebo group = 27/21/11/1 Each child was seen in outpatients department once every 7 to 10 days. At each visit drug compliance was reviewed and assessments for muscle relaxation, motor function and well being of the child were carried out. The caregiver was taught the passive stretching exercises for the child and advised to administer the bedtime medications. Results were obtained 15 to 20 days after therapy started. **Intervention Group** Half dose diazepam group n=60 children under 8.5kg given 0.5mg daily at bedtime children over 8.5kg given 1mg daily at bedtime				

	Full dose diazepam group n=60 children under 8.5kg given 1mg daily at bedtime children over 8.5kg given 2mg daily at bedtime				

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Authors Mathew,A., Mathew,M.C. 2005b **Year of publication** 2005 **Study location** India **Ref ID** 56488 **Type of study** Randomised controlled study **Aim of study**	**Inclusion Criteria** Serially recruited children with spastic CP who attended the outpatients department of a developmental paediatrics unit and who weighed under 15kgs **Exclusion Criteria** Child had received muscle relaxants Child weighed over 15kgs **Baseline characteristics** 120 recruited children were randomised into two groups of 60 participants. At baseline there was no significant difference between the two groups for the following characteristics: Age up to 5 years Diazepam group = 57/60 Placebo group = 54/60 Sex (no of girls) Diazepam group = 24/60 Placebo group = 23/60 Socioeconomic status (High/Upper	**Intervention** Packets of diazepam prepared by the Pharmacy Department. Single dose of diazepam given to children at bedtime, but size of dose given is not stated. **Comparison 1** Packets of placebo, identical in appearance to the diazepam packets prepared by the Pharmacy Department. Single dose of placebo given to children at bedtime.	**Outcome 1** All outcomes were assessed at the first visit and reviewed in all children after 15-20 days of receiving either diazepam or placebo. 1) Disposition of the child during activities of daily living: Detailed enquiries to ascertain and score the well-being of the child during the daily activities like feeding, bathing, playing, exercising and sleeping were made. The disposition of the child during the activity was graded from 0-5 on a scale with aa spectrum ranging from usually pleasant and happy to unhappy, persistently fretful and disturbed. Mean change in score from baseline Diazepam group = 6.31 SD±1.94 n=59 Placebo group = 0.38 SD± 0.62 n=55 2) Burden of caring for the child on the family: The burden of caring for the child on the family was found out from the information given by the mother or chief care-giver. The frequency of occurrence of the difficulties described below was the index of scoring the child on a scale from 0-7 i) Attention demand on caregiver due to inconsolable daytime crying spells ii) Disturbed sleep for caregiver due to frequent waking at night iii) Extended time requirement for feeding due to crying during meal-times iv) Caregiver's pesence required to carrry/comfort fretting child in waking hours v) Physical therapy stressful due to crying when limbs are moved Mean change in score from baseline Diazepam group = 7.75 SD±1.98 n=59 Placebo group = 0.44 SD± 0.66 n=55	Limitations Allocation concealment : computer randomisation Participants blinded to intervention : yes Carers blinded to intervention : yes Investigators blinded to intervention : yes Number of participants not completing treatment : 6 (1 from treatment group and 5 from placebo group) Number of participants with no available outcome data : 6 Selective outcome reporting : unclear Any other limitations : Outcomes are reported clearly but are not validated tools. No aim of the study or sample size calculation are reported, therefore it is difficult to tell whether there has been selective	**Funding** Not stated **Other information** Ethical approval : Research and Ethics Committee of the Christian Medical College and Hospital, Vellore Informed consent : Yes Sample size : not given **Selective outcome reporting** - **Sample size** -

	/Middle/Low) Diazepam group = 2/12/16/30 Placebo group = 5/9/18/28 Grade of cerebral palsy according to functional limitation of physical activity (Mild/Moderate/Severe) Diazepam group = 0/16/44 Placebo group =1/13/46 Type of cerebral palsy (diplegia, hemiplegia, triplegia, double hemiplegia, quadruplegia) Diazepam group = 17/8/5/0/30 Placebo group = 7/8/4/5/36 All mothers or caregivers were shown different passive movements (stretching programme) that could be easily carried out regularly at home from the 5th day of starting the drug trial. **Intervention Group** n=60		3) Child's behavioural profile: The frequency of undesirable behaviour given below during the time of clinical examination was observed and graded by the investigator as rarely =0, occasionally = 1, some of the time = 2, most of the time = 3, continuously = 4 vi) irritability vii) crying for reasons other than for vegetative needs viii) non-compliance ix) resistance to movement of limbs x) wanting to be carried xi) disinterest xii) drowsiness Mean change in score from baseline Diazepam group = 8.17 SD±2.14 n=59 Placebo group = 0.82 SD± 1.07 n=55 4) Adverse effects : no episodes of daytime drowsiness reported in either group **Outcome 2** - **Outcome 3** -	reporting of outcomes Indirectness Population : None Intervention : None Comparison : None Outcomes assessed : None	

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Authors Joynt,R.L., Leonard,J.A.,Jr. **Year of publication** 1980 **Study location** USA **Ref ID** 56533 **Type of study** Randomised controlled study **Aim of study** To evaluate the physiological activity, safety and side-effects of dantrolene sodium suspension in children	**Inclusion Criteria** Children with cerebral palsy from a pediatric rehabilitation clinic Able to participate in the study Spasticity interfering with function Neurologically and psychologically stable at the time they entered the study **Exclusion Criteria** Unclear **Baseline characteristics** 20 children -Total sample characteristics (not broken down by group in study): a. sex: 8 girls, 12 boys b. age rage: 4 to 15 years c. diagnoses: Spastic diplegia: 7 spastic quadriplegia: 7 spastic hemiplegia: 5 spastic parapegia: 1 Etiology in the patient with paraparesis was undetermined: this child	**Intervention** Dantrolene sodium was administered for a total time of 6 weeks It was provided in a 5mg/cc suspension and was administered by a calibrated dropper or measuring cup, as appropriate. Following initial evaluation at visit l, treatment was begun with a drug dosage of 4mg/kg/day and was increased gradually during the next three weeks to an optimum level, 12mg/kg/day being the approximate maximum The children were re-evaluated after three weeks (visit 2) and dosage was adjusted to an optimum level depending on the results of the history and physical examination at that time, and was then maintained at this level until visit 3 (six weeks after initiating treatment) The drug was then discontinued and the children were tested again three weeks later (visit 4) Other medications were not altered during the treatment period. Concomitant medications included mephobarbital, phenobarbital, phenytoin, antibiotics, decongestants, vitamins, imipramine and (in one patient) diazepam	**Outcome 1** Strength of voluntary plantar flexion (Positive numbers = increase; negative numbers = decrease. Strength measured in foot/pounds of torque generated by plantar flexion againts a foot-plate) a. after 6 weeks -dantrolene: < -0.2 (8); -0.2 (0); > -0.2 (0) -placebo: < -0.2 (1); -0.2 (1); > -0.2 (5) p=0.003 b. after 9 weeks -dantrolene: < -0.8 (6); -0.8 (0); > -0.8 (3) -placebo: < -0.8 (1); -0.8 (0); > -0.8 (4) NS **Outcome 2** Spasms (number of children) - a. after 3 weeks -dantrolene: improved: 3 no change: 8 -placebo: improved: 0 no change: 9 p=0.089 It is reported that spasms were not subsequently reduced in the intervention group but no more figures are provided. Spasms were rated by the severity of muscle contractions that were produced in other areas during the range-of-motion examination of a joint of one of the extremities. Mild spasms (rated 1) would include motion at another joint, such as knee flexion or extension occurring while the ankle was	Limitations Allocation concealment : pharmacy controlled Participants blinded to intervention : yes Carers blinded to intervention : yes Investigators blinded to intervention : yes Number of participants not completing treatment : 2 one from each group of total n=21 patients Number of participants with no available outcome data : 1 from placebo group Selective outcome reporting : yes Any other limitations : small sample size Indirectness Population : None Intervention : None Comparison : None Outcomes assessed : Unvalidated measures used	**Funding** Eaton Laboratories and the Norwich Pharmacal Company provided the drug and also financial assistance **Other information** - **Selective outcome reporting** Yes, as 61 variables were studied including 36 timed variables for testing function and mobility of extremities Besides some the outcomes reported were measured during the three assessment visits but only results from one or two of those visits were reported **Sample size** Small sample size, no calculation performed

	presented at nine years with progressive spastic paraparesis, not strictly cerebral palsy in the usual sense At baseline intervention and comparison group were statistically similar, except that those in the intervention group were "somewhat" stronger **Intervention Group** n=11	**Comparison 1** Placebo (no other details reported) Other medications were not altered during the treatment period. Concomitant medications included mephobarbital, phenobarbital, phenytoin, antibiotics, decongestants, vitamins, imipramine and (in one patient) diazepam	being examined. Severe spasms (rated 3) were, for example, a mass flexion pattern of the trunk and arms occurring while a leg was being examined. The scores for a given result from each extremity were totalled to produce the final score assigned to that particular examination. **Outcome 3** -Unscrewing medium-sized barrels (time in secs) - (Positive numbers = improved negative numbers = worsened) a. after 6 weeks - dantrolene: < -0.3 (4); -0.3 (1); > -0.3 (5) -placebo: < -0.3 (5); -0.3 (0); > -0.3 (4) NS b. after 9 weeks -dantrolene: < -0.15 (5); -0.15 (0); > -0.15 (6) -placebo: < -0.15 (5); -0.15 (0); > -0.15 (4) NS -Left arm vertical alignment of buttons (elbow flexion-extension, time in secs) - (Positive numbers = improved negative numbers = worsened) a. after 6 weeks -dantrolene: < 0 (7); 0 (0); > 0 (3) -placebo: < 0 (2); 0 (1); > 0 (6) p= 0.051 b. after 9 weeks -dantrolene: < -0.095 (6); -0.095 (0); > -0.095 (5) -placebo: < -0.095 (4); -0.095 (0); > -0.095 (5) NS -Unbuttoning medium-sized buttons (time in secs) - (Positive numbers = improved negative numbers = worsened) a. after 6 weeks		

			-dantrolene: < 0.3 (7); 0.3 (0); > 0.3 (2) -placebo: < 0.3 (2); 0.3 (0); > 0.3 (7) p=0.028 b. after 9 weeks -dantrolene: < 0.2 (5); 0.2 (0); > 0.2 (6) -placebo: < 0.2 (3); 0.2 (0); > 0.2 (6) NS <u>-Buttoning small-sized buttons (time in secs)</u> (Positive numbers = improved negative numbers = worsened) a. after 6 weeks -dantrolene: < 0 (4); 0 (2); > 0 (4) -placebo: < 0 (0); 0 (4); > 0 (5) p=0.054 b. after 9 weeks -dantrolene: < 0 (2); 0 (4); > 0 (5) -placebo: < 0 (1); 0 (5); > 0 (3) NS		

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Authors Denhoff,E., Feldman,S., Smith,M.G., Litchman,H., Holden,W. **Year of publication** 1975 **Study location** USA **Ref ID** 56537 **Type of study** Some other intervention type **Aim of study** To evaluate the effects of dantrolene sodium in children with spastic cerebral palsy	**Inclusion Criteria** Unclear (apart from children with cerebral palsy) **Exclusion Criteria** Unclear **Baseline characteristics** Total: 28 children Sex: 16 boys, 12 girls Age range: 18 months to 12 years (mean 7 years) Types of cerebral palsy: -spastic quadriplegia: 15 -spastic hemiplegia: 7 -spastic diplegia: 4 -mixed spasticity and athetosis: 1 -mixed spasticity and rigidity: 1 Degrees of severity: -mild: 14 -moderate: 5 -severe: 9 21 of the children were participating in the Meeting Street School's daily service program for multi-handicapped children; the other	**Intervention** Dantrolene sodium ('Dantrium') administered orally in suspension form containing 25mg per 4ml for six weeks each group with a washout period of two weeks in between. Drug dosage was begun at 1mg/kg q.i.d. (4mg/kg/24hrs) and was increased by 1mg/kg at weekly intervals up to a maximum dose of 3mg/kg/dose (12mg/kg/24hrs) at the beginning of the third week of treatment. This dosage was then continued for the remaining three weeks of the drug-treatment period. <u>Note:</u> At least two weeks prior to the beginning of the study, 3 children had their diazepam discontinued. During the study, 8 children were maintained on various drugs: one each on diphenylhydantoin, phensuximide, phenobarbital and promethazine and two each on primidone and methylphenidate **Comparison 1**	**Outcome 1** Measurements in all areas were made before treatment began, at the end of each treatment period and during the 'washout' period. Additional evaluations of motor performance, activities of daily living and general behaviour were made at two points within each treatment period. Only treatment difference scores were reported, but not raw data for individual measurements 1) Neurological measurements Included: muscle strength, spasticity, tendon jerk reflexes and clonus in both upper and lower extremities Measured by: paediatric neurologist Unit of measurement: an objective system of clinical evaluation was used (unclear which one) and values were assigned to the evaluations in a standardised manner 2) Orthopaedic measurements Included: active and passive range of motion in the major joints (shoulder, elbow, hip, knee) Measured by: orthopaedist Unit of measurement: degrees of movement 3) Motor performance Included the time, distance and/or errors in: leg-spread over a barrel crawling or walking on a plank precision of foot placement forward and lateral reaching on a table stacking blocks rotation of a wheel, calibrated in degrees, which measures range of motion in the shoulder	Limitations Allocation concealment : unclear Participants blinded to intervention : yes Carers blinded to intervention : yes Investigators blinded to intervention : yes Number of participants not completing treatment : 0 Number of participants with no available outcome data : 9 Selective outcome reporting : yes (orthopaedic data could not be converted from raw scores to treatment change and treatment difference scores-according to authors-therefore not reported) Any other limitations : validity of instruments used to measure most of the outomes is unclear	**Funding** Grant from Eaton Laboratories, Division of Morton-Nonvich Products Inc., Nonvich, New York. **Other information** Informed consent? : unclear Ethical approval? : unclear Sample size calculation? : no **Selective outcome reporting** - **Sample size** -

	seven had attended the school previously, and came back at regular intervals for evaluation. **Intervention Group** -	An identical volume of placebo was administered during the non-drug treatment period	Measured by: physical therapist 4) Measurements by program staff (Only in 21 children attending Meeting Street School) Activities of daily living included: co-ordination of movement in dressing and eating control of limbs in spontaneous play stamina for daily activities freedom of movementfacilitation of therapy 'body anxiety' in space (fear of change of position) Behavioural ratings included: attention and distractibility activity level and emotionality' (e.g. irritability, temper tantrums, intolerance of frustration, fearfulness, crying episodes) Unit of measurement: a five-point scale of activities of daily living and behavioural functioning (no other details provided) 5) Parental measurements Activities of daily living and behavioural functioning as previous but excluding the measurement of 'body anxiety' Unit of measurement: a five-point scale of activities of daily living and behavioural functioning (no other details provided) In calculating scores for parental and staff evaluations, ratings obtained during the later parts of the treatment periods were weighted more heavily, on the assumption that heavier dosages at those times should have more significance attached to them **Outcome 2** 6) Paediatric evaluations Clinical determination (assume it means history taking and physical examination but unclear) Measured by: paediatrician regularly during the study Laboratory determinations included:complete blood counts urinalysis biochemical tests (creatinine and creatinine phosphokinase	Indirectness Population : none Intervention : none Comparison : none Outcomes assessed : some measurements were grouped under an "umbrella" outcome category which is not directly applicable to clinical practice. For example neurological measurement grouped together muscle strength and spasticity which are not necessarily clinically related. Activities of daily living and behaviour rating were also grouped under one single outcome without any clinical rationale supporting this decision	

			levels) 7) Adverse effects during formal study period Noted in 23 of the 28 children, but generally transient and disappeared within a week Included: irritability, lethargy, drowsiness and general malaise. Irritability was reported more often during placebo periods than during drug periods 16 children showed adverse effects during dantrolene periods and 7 during placebo periods ($p < 0.03$) 8) Adverse effects after formal study period Four of the nine children in whom the drug was continued after the completion of the formal study developed or had exacerbations of seizures. One nine-year-old boy who had been treated with dantrolene during the first treatment period showed laboratory evidence of elevated serum levels of liver enzyme two months after last receiving medication. His SCOT was 90 units (normal 11 to 52). A further determination 10 days later was 116 units. At no time did he show clinical signs or symptoms of hepatitis. **Outcome 3** Number of children showing changes in functioning between dantrolene and placebo (ΔD – ΔP) Changes a. Neurological Marked: ΔD (4); ΔP (0) Moderate: ΔD (2); ΔP (2) Marginal: ΔD (7); ΔP (2) Total changes: ΔD (13); ΔP (4) No changes: 11 P<0.04 b. Motor Marked: ΔD (0); ΔP (2) Moderate: ΔD (5); ΔP (4) Marginal: ΔD (5); ΔP (2)		

			Total changes: ΔD (10); ΔP (8) No changes: 8 P= N.S c. Staff Marked: ΔD (4); ΔP (0) Moderate: ΔD (4); ΔP (0) Marginal: ΔD (3); ΔP (2) Total changes: ΔD (11); ΔP (2) No changes: 9 P<0.02 d. Parents Marked: ΔD (5); ΔP (1) Moderate: ΔD (4); ΔP (2) Marginal: ΔD (3); ΔP (0) Total changes: ΔD (12); ΔP (3) No changes: 13 P<0.03 <u>Notes:</u> Significance levels were determined by the binomial distribution. Changes: Marked treatment-difference score (3) indicated a 3-point spread or larger between scores in drug and placebo periods. For example, during drug period a child may have shown marked change compared with baseline period (+ 3) but no measurable change during placebo period (0). Treatment difference score of 3 between periods. Again, a child may have shown moderate changes during drug period compared with baseline (+ 2) but showed poorer functioning during placebo period (-1), also giving a marked (+ 3) treatment-difference score		

Bibliographic details	Number of Participant Participant Characteristics	Intervention characteristics	Outcome measures and results	Quality assessment	Reviewer comment
Authors Haslam,R.H., Walcher,J.R., Lietman,P.S., Kallman,C.H., Mellits,E.D. **Year of publication** 1974 **Study location** USA **Ref ID** 58561 **Type of study** Randomised controlled study **Aim of study** To investigate the potential of dantrolene as a therapeutic agent in children with spasticity	**Inclusion Criteria** Children with upper neuron signs admitted to the John F kennedy Institute. Spasticity was defined as "an initial resistance to an extremity of passive movement, followed by a sudden giving way - the claspknife phenomenon" **Exclusion Criteria** No details given **Baseline characteristics** Age range 1.5 to 17 years (mean 6.5 years) IQ range : 10 to 80 (mean 45) Sex : 18/26 Some children took anticonvulsants, however, all muscle relaxant drugs were discontinued for at least 2 weeks before the beginning of the study **Intervention Group** -	**Intervention** On the day of admission a neurological examination, laboratory evaluation, urinalysis, serum GOT, serum GPT, alkaline phosphatase, bilirubin, calcium, phosphorus, serum urea nitrogen, creatinine and serum electrolytes were performed. On the second day the participant started their pre-assigned intervention for 14 days. There was a 10 day wash out period between interventions and the second treatmennt period was 15 days. Dantrolene was given orally before meals, four times a day in a flavoured suspension containing a concentration of 5mg/ml. Dosages began at 1mg/kg and were increased to a maximum of 3mg/kg or 12/mg/kg/day **Comparison 1** A placebo (indistinguishable from the drug) was given orally before meals, four times a day in a flavoured suspension.	**Outcome 1** Examinations took place on days 4, 8, 11 and 15 of each treatment period as well as two evaluations performed in the washout phase. Neurological assessment made by one of two alternating examiners. Spasticity was graded on a scale according to severity of clonus, passive movement, spontaneous movement, tone, reflexes and scissoring. This was then revised to a quantitative score 1) Scissoring mean improvement score : (none = 1, minimal = 2, moderate = 3, marked = 4) during dantrolene treatment mean improvement score signifcantly different from baseline : <0.01 during placebo treatment mean improvement score did not signifcantly differ from baseline : >0.05 Mean difference in improvement score between dantrolene and placebo groups = 0.381 p>0.05 2) Muscle tone mean improvement score (range subnormal or hypotonia = 1 to marked increase or hypertonia = 8) during dantrolene treatment mean improvement score signifcantly different from baseline : <0.005 during placebo treatment mean improvement score did not signifcantly differ from baseline : >0.05 Mean difference in improvement score between dantrolene and placebo groups = 0.609 p<0.05 **Outcome 2** - **Outcome 3** -	Limitations Allocation concealment : Adequate Participants blinded to intervention : Yes Carers blinded to intervention : Yes Investigators blinded to intervention : Yes Number of participants not completing treatment : 3/26 Number of participants with no available outcome data : 3/26 Selective outcome reporting : Yes, "self help skils" outcome data are not reported though referred to Any other limitations : Investigators tried to account for unwillingess of children to co=-operate by developing a spasticity scale. This did not lend itself to statistical analysis and another scoring system was used. The	**Funding** Not stated. Acknowledgement given to Eaton Laboratories for its support, however no further details are provided **Other information** Informed consent? : not stated Ethical approval? : not stated Sample size calsulation?: not stated **Selective outcome reporting** - **Sample size** -

				authors believe that the effect of dantrolene was underestimated because of the range of different children seen in their group and because of insufficiently sentitive scales being used. Indirectness Population : none Intervention : none Comparison : none Outcomes assessed : Muscle tone outcome measurement is not Ashworth or modified Ashworth scale.	

Bibliographic details	Number of Participant Participant Characteristics	Intervention characteristics	Outcome measures and results	Quality assessment	Reviewer comment
Authors McKinley,I., Hyde,E., Gordon,N. **Year of publication** 1980 **Study location** UK **Ref ID** 58566 **Type of study** Randomised controlled study **Aim of study** To conduct a crossover double blind RCT to assess the effects of baclofen on everyday activities.	**Inclusion Criteria** Children with spasticity attending a day school for physically handicapped children **Exclusion Criteria** Not stated **Baseline characteristics** Of 20 included children, All children had a degree of spasticity, but six had a mixed cerebral palsy : 5 had choreoathetosis and 3 had ataxia. There was an even sex distribution, the age range was 7-16 years. Half of the children were believed to be within the range of average intelligence, but three were severely mentally handicapped. Two children had a history of epilepsy and were on regular anticonvulsants. No other children received medication throughout the trial. **Intervention Group** -	**Intervention** Tablets were given at specified times by the school nurse or by parents in response to weekly written instructions. The dosage of baclofen given in three divided doses in each period was 0.5mg/kg, 1mg/kg, 2mg/kg, and 1mg/kg each for one week. No child exceeded 60mg/kg/day. There was a two week wash out period between treatment periods. **Comparison 1** Tablets were given at specified times by the school nurse or by parents in response to weekly written instructions. No further details are stated	**Outcome 1** In addition to the 9-weekly standard examination and test, weekly reports of behaviour, recorded by parent, teachers and therapists were obtained. Children were examined at the same time at the end of each week by the investagators, where possible by the same investigator each week. 1) Muscle tone : Reduced muscle tone or better movement measured on the Ashworth scale baclofen period : 14/19 placebo period : 5/19 unchanged throughout n=1 (p=0.064) 2) Gait assessment baclofen period : 8/12 placebo period : 4/12 unchanged throughout n=8 (p = NS) 3) Side effects The parents of 9 children reported side effects baclofen period : 8 - In 4 of these children reduction of dose relieved side effects placebo period : 1 Overall, side effects reported were drowsiness (5), sickness (2), dizziness (2), nocturnal enuresis (2), absence states, query epliptiform (2) slurred speech (2) and weakness (1) Therapists and teachers reported drowsiness in 12 children during the trial : all were taking baclofen at the time (p<0.001) and had shown reduced tone or improved movement 4) Would wish their child to continue on active treatment (if parents' guess correct)? 1/20 parents	Limitations : Allocation concealment : unclear, not specified Participants blinded to intervention : yes Carers blinded to intervention : yes Investigators blinded to intervention : yes Number of participants not completing treatment : 2/20 Number of participants with no available outcome data : 2/20 although most data available Selective outcome reporting : Any other limitations : Indirectness : Population : None Intervention : None Comparison : None Outcomes : None	**Funding** not stated **Other information** Informed consent? : Yes Ethical approval? : Local ethical committee Sample size calculation : No **Selective outcome reporting** - **Sample size** -

			Outcome 2 - **Outcome 3** -		

Bibliographic details	Number of Participant Participant Characteristics	Intervention characteristics	Outcome measures and results	Quality assessment	Reviewer comment

Authors Rice,J., Waugh,M.C. **Year of publication** 2009 **Study location** **Ref ID** 59380 **Type of study** **Aim of study** To evaluate the effect of high-dose trihexyphenidyl on change in overall dystonia severity, with secondary outcomes assessed of change in upper limb function and achievement of individualized goals	**Inclusion Criteria** Children aged between 2 and 18 years with predominant dystonic cerebral palsy, verified by one of the study physicians. Not treated with trihexyphenidyl or another anticholinergic medication in the previous 3 months and use of other treatments such as oral baclofen or intrathecal baclofen at a stable dose for 3 months and unlikely to be altered **Exclusion Criteria** Planned change in therapy program over the duration of the study (6 months). Surgical or medical interventions such as orthopaedic surgery or botulinum toxin injections scheduled during the study or in the 6 months prior to study entry **Baseline characteristics** 16 children Median age: 7.9 years (range 2-17 years) Sex: 10 males and 6 females	**Intervention** Trihexyphenidyl for 12 weeks. Dose escalation according to the following schedule: Week 1 0.2 mg/kg/d in 3 divided doses Week 2 0.5 mg/kg/d in 3 divided dose Week 3 1.0 mg/kg/d in 3 divided doses Week 4 1.5 mg/kg/d in 3 divided doses Week 5 2.0 mg/kg/d in 3 divided doses Week 6 2.5 mg/kg/d in 3 divided doses Week 7-12 2.5 mg/kg/d in 3 divided doses Week 13-16 Washout Adjustments were made to the dose of medication in a stepwise manner if any significant symptoms or side effects related to the medication were encountered Washout period: 4 weeks **Comparison 1** Placebo for 12 weeks Placebo was matched in colour, odour and taste to the active medication Same dose escalation as in medication Washout period: 4 weeks	**Outcome 1** Assessments were performed at baseline, 12, and 28 weeks after commencement. Method: videotaping the child in his or her usual sitting or standing position and recording resting and active limb movements over several minutes in each body region in a standardized fashion. Recorded activities included those listed as target areas for functional change as well as the protocol for the Quality of Upper Extremity Skills Test. This video was coded to allow subsequent random order of scoring Who measured: A blinded occupational therapist trained in the use of the Barry-Albright Dystonia scale (BAD) At the baseline visit, a physician member of the research team performed a comprehensive medical assessment including review of abnormal muscle tone and distribution. Instruments: The Barry-Albright Dystonia scale <u>BAD (mean score, 95% CI)</u> Baseline: 18.4 (15.5 to 21.2) Placebo: 16.9 (13.4 to 20.4) Triehxy: 18.3 (14.8 to 21.8) Change: 0.9 (-2.2 to 3.9) <u>Analysis of effects</u> Treatment: F (1, 12) =0.2, p=0.67 Carry: F (1, 12) = 1.7, p=0.22 Order: F (1, 12) =0.3, p=0.57 **Outcome 2** Assessments were performed at baseline, 12, and 28 weeks after commencement 1. Assessment of upper limb function Method: videotaping the child in his or her usual sitting or standing position and recording resting and active limb	Randomisation and allocation concealment: After recruitment, children were randomly assigned using a randomization table generated by the hospital pharmacy to initial treatment with either placebo medication or active medication (trihexyphenidyl). Balanced randomization was performed by the hospital pharmacist, who also kept these codes concealed until data collection was complete. Active medication was constituted in a concentration of 10 mg/mL. Both medications were matched in color (green), odor (aniseed), and taste (bitter). Medication A was the phase 1 treatment and	**Funding** Unclear **Other information** Informed consent A legal guardian gave written informed consent before entry into the study Ethical approval Study was approved by the Ethics Committee of the Children's Hospital at Westmead Instruments used: According to the authors reliability, validity, and responsiveness have been demonstrated for the Quality of Upper Extremity Skills Test and the Canadian Occupational Performance Measure **Selective outcome reporting** No **Sample size** Sample size is small but the study was designed as a pilot study and as such a power calculation was not performed Authors estimated

	Type of cerebral palsy according to the Gross Motor Function Classification System: 2 children: Level III (13%) 3 children: Level IV (19%) 11 children: Level V (69%) 11 children (69%) had associated spasticity **Intervention Group**		movements over several minutes in each body region in a standardized fashion. Recorded activities included those listed as target areas for functional change as well as the protocol for the Quality of Upper Extremity Skills Test. This video was coded to allow subsequent random order of scoring Who measured: A blinded occupational therapist trained in the use of the Quality of Upper Extremity Skills Test Instrument: Quality of Upper Extremity Skills Test (QUEST) <u>QUEST (mean score, 95% CI)</u> Baseline: 15.3 (–0.1 to 30.7) Placebo: 15.1 (2.8 to 27.4) Trihexy: 13.5 (1.4 to 25.5) Change: –1.6 (–6.3 to 3.1) <u>Analysis of effects</u> Treatment: F (1, 12) =0.9, p=0.37 Carry: F (1, 12) =1.4, p=0.25 Order: F (1, 12) =0.2, P= 0.90 2. Other functional goals Instruments, methods and who measured: Families completed the Canadian Occupational Performance Measure (COPM) with an experienced occupational therapist. A change score of 2 or more is considered clinically significant. The assessment then directed the family and occupational therapist to identify up to 5 functional goals for the Goal Attainment Scale to measure change Participants and their caregivers selected a total of 80 goals, averaging 5 goals per participant. The goals covered the following areas: mobility and posture, dressing, feeding, toileting and play skills, including the use of switching for communication. Goal Attainment Scale (GAS) scores were converted to a normalized T-score, with the baseline score set at 20	medication B, the phase 2 treatment. The bottles were identical apart from the labels A and B. Participants blinded to intervention: Yes Carers blinded to intervention: Yes Researchers blinded to intervention: Yes Indirectness: Population: some. Only 11/16 children had associated spasticity Intervention: none Comparison: none Outcomes: some? Canadian Occupational Performance Measure - Is this used in the UK?	that within the scope of the study it was feasible to recruit 15-20 participants into the trial However it is unclear why if a total of 55 children were invited to participate only the first 16 children who were subsequently seen and met entry criteria were recruited into the study

			GAS Mean Score (95% CI) Baseline: 20.0 Placebo: 33.3 (27.4 to 39.1) Trihexy: 39.3 (31.8 to 46.8) Change: 6.8 (-3.7 to17.5) Analysis of effects Treatment: F (1, 11) = 1.7, p=0.22 Carry: F (1, 11) = 0.0, p=0.89 Order: F (1, 11) = 10.2, p= 0.009 COPM (Satisfaction) (95% CI) Baseline: 2.3 (1.8 to 2.7) Placebo: 3.8 (2.8 to 4.8) Trihexy: 4.7 (3.5 to 5.9) Change: 0.7 (-0.3 to 1.8) Analysis of effects Treatment: F (1, 10) = 1.5, p=0.24 Carry: F (1, 10) = 0.6, p=0.45 Order: F (1, 10) =1.1, p= 0.31 COPM (Performance) (95% CI) Baseline: 2.6 (2.2 to 3.0) Placebo: 3.8 (3.0 to 4.7) Trihexy: 4.4 (3.6 to 5.3) Change: 0.8 (-0.5 to 2.0) Analysis of effects Treatment: F (1, 12) =2.2, p=0.17 Carry: F (1, 12) =0.1, p=0.72 Order: F (1, 12) =4.7, p=0.05 **Outcome 3** Adverse effects How measured: the child's guardian was contacted weekly by telephone to review any problems encountered during the trial, and adverse effects were recorded systematically on the results proforma Who measured: unclear, but one of the rehabilitation physicians		

			was available 24 hours a day to manage medication adverse effects Adverse effects symptoms occurred in all children during the active medication phase and included: agitation (distressed without reason or other odd behaviour) constipation dry mouth poor sleep One child developed multiple adverse effects related to trihexyphenidyl (including dry mouth, confusion, agitation, inability to sleep, tachycardia, hallucinations, and urinary incontinence), requiring brief admission to hospital after the initial dose and had to withdraw from the trial The second child withdrew after 8 weeks due to a family crisis unrelated to medication dosing Peak doses ranged from 0.05 to 2.60 mg/kg/d. The maximum dose achieved on active medication was 70 mg/d Symptoms while on placebo were recorded in 6/16 (38%) of children Overall perception of the medication trial and overall satisfaction with the study Families completed questionnaires at the end of phases 1 and 2 Despite the frequency of side effects, most parents or carers (81%) indicated that they were satisfied with their child's participation in the study, indicating that even if their child did not respond to the medication this in itself was useful information for them. Some parents and carers indicated altruistically that their participation in the study may assist other children with the treatments.		