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Title:

Pharmacological management of abnormal tone and movement in Cerebral Palsy:

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Abstract (233/250)

Background: The evidence base to guide pharmacological management of tone and abnormal movements in Cerebral Palsy (CP) is limited, as is an understanding of routine clinical practice in the UK. We aimed to establish details of motor phenotype and current pharmacological management of a representative cohort across a network of UK tertiary centres.

Methods: Prospective multi-centre review of specialist motor disorder clinics at 8 UK centres, collecting data on clinical features and pharmacological management of children and young people (CYP) with CP over a single calendar month.

Results: Data was collected from 275 CYP with CP reviewed over the calendar month of October 2017. Isolated dystonia or spasticity was infrequently seen, with a mixed picture of dystonia and spasticity +/-

choreoathetosis identified in 194/275 (70.5%) of CYP.A co-morbid diagnosis of epilepsy was present in 103/275 (37.4%). The most commonly used medications for abnormal tone/movement were baclofen, trihexyphenidyl, gabapentin, diazepam and clonidine. Medication use appeared to be influenced separately by the presence of dystonia or spasticity. Botulinum toxin use was common (62.2%). A smaller proportion of children (12.4%) had undergone a previous neurosurgical procedure for tone/movement management.

Conclusions:

CYP with CP frequently present with a complex movement phenotype and co-morbid epilepsy. They have multiple therapy, medical and surgical management regimens. Future trials of therapeutic, pharmacological or surgical interventions in this population must adequately encompass this complexity in order to be translatable to clinical practice.

Introduction

Cerebral Palsy (CP) is the commonest form of chronic neurodisability encountered in paediatric practice and may be defined as a clinical syndrome of "*permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain"(1)*. Elevated tone and involuntary movements are typically experienced by Children and Young People (CYP) with CP. Elevated tone, or hypertonia, caused by abnormal

muscle contraction may be due to spasticity, dystonia, rigidity, or a variable combination of these pathological findings(2). The most widely adopted classification system for CP is the Surveillance of Cerebral Palsy in Europe (SCPE) classification(3), which classifies CYP on the basis of the Predominant Motor Type. On this basis, 80-95% of CYP with CP are considered to have "spastic" CP, and 5-17% the "Dyskinetic" form (dystonia +/- choreoathetosis)(4, 5). One limitation of this system is that spasticity and dystonia are treated as mutually exclusive, when in reality they are often co-incident in children with motor disorders(6-8).

Elevated tone and involuntary movements typically interfere with independent function and participation, the delivery of daily care and overall quality of life. Consequently, pharmacological interventions are commonly prescribed, though the evidence base to guide the clinician's choice of most appropriate medication is currently extremely limited. The recent American Academy of Cerebral Palsy and Developmental Medicine (AACPDM) guidelines on the management of dystonia in CP concluded that there was insufficient evidence to support any oral pharmacological agent, instead basing recommendations entirely upon expert opinion(9). A number of recent reviews of the management of Dyskinetic CP have highlighted the paucity of high quality evidence in this patient group (9-11). The National Institute for Health and Care Excellence in the UK has produced guidelines for the management of spasticity in CYP(12), as has the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society in the US(13). In both cases, a paucity of high quality

evidence was identified for enteral pharmacological interventions in particular.

Taken collectively, there is a pressing need for better quality evidence to guide the pharmacological management of CYP with CP. CP is a heterogeneous disorder, in terms of the nature of the underlying brain injury, pattern of motor difficulties, functional impairments and medical co-morbidities experienced. This heterogeneity creates challenges for the design of definitive interventional studies, as does the current limited knowledge of pharmacological management in current clinical practice beyond the recommendation of experts(14, 15).

In preparation for designing future trials of pharmacological management of abnormal tone and movement in CYP with CP we performed a prospective multi-centre review in the outpatient setting over a calendar month. We aimed to determine:

- The clinical characteristics of CYP with CP seen during this snap shot of clinical practice, focusing particularly on their pattern of motor abnormalities
- Current pharmacological management of abnormal tone and movement
- Diagnosis of co-morbid epilepsy and its management
- Determination of factors such as botulinum toxin use which could confound future potential enrolment in pharmacological studies.

Method

A prospective evaluation of CYP with a clinical diagnosis of CP seen in tertiary paediatric neurology/neurodisability motor disorder clinics at 8 UK centres (Evelina London Children's Hospital, Great Ormond Street Hospital, Great North Children's Hospital, University Hospitals Bristol, Alder Hey Children's Hospital, Leeds Teaching Hospital, Royal Belfast Hospital for Sick Children, John Radcliffe Hospital and Sheffield Children's Hospital) was undertaken. Data was recorded from all cases seen over the calendar month October 2017, using a standardised data pro-forma. Data included details of gender, age, Gross Motor Classification System (GMFCS) level(16), Manual Ability Classification System (MACS) level(17), current medication use, diagnosis of co-morbid epilepsy, and whether the CYP had undergone a neurosurgical intervention aimed at reducing tone and/or abnormal movements - namely Deep Brain Stimulation (DBS), intrathecal baclofen (ITB) pump insertion, or Selective Dorsal Rhizotomy (SDR). The presence/absence of dystonia and/or spasticity was determined using the Hypertonia Assessment Tool (18), as outlined in Box 1. The presence of choreoathetosis as defined by the Taskforce for Childhood Movement disorder (19) was also recorded (Box 1). For all three motor abnormalities, clinicians were asked to record whether this was clinically significant. This was a subjective judgment, based on whether the recording clinician felt that the motor abnormality interfered sufficiently with function and participation, delivery of daily cares and/or quality of life to require an intervention aimed at its reduction. Descriptive statistics were used to summarise the data, with analysis performed on SPSS Version 24.

Results

Data was collected from a total of 275 CYP with CP (162 male), median age 9 years (Range 1-18 years, 5 to 9 years, 25th-75th Centile). Clinico-demographic features are shown in Table 1. Both GMFCS (available for all 275 cases) and MACS levels (available for 258/275 cases) demonstrated peaks at Level II and Level V (Figure 1(a)). Details of motor phenotype are illustrated in Figure 1(b). Spasticity was identified in 242/275 (88.0%) CYP, judged clinically significant in 176/242 (72.7%). Dystonia was identified in 222/275 (80.7%) CYP; this was judged to be clinically significant in 172/222, 77.4%). Choreoathetosis was identified in 75/275 (27.2%) CYP (clinically significant in 26/75 (34.6%).

Isolated spasticity was identified in only 47/275 (17.1%) CYP, isolated dystonia in 16/275 (5.8%) CYP, with no CYP demonstrating isolated choreoathetosis. A mixture of spasticity and dystonia was identified in 132/275 (48.0%) CYP, dystonia and choreoathetosis in 12/275 (4.4%) CYP and spasticity and choreoathetosis in 1/275 (0.4%) CYP. A combination of spasticity, dystonia and choreoathetosis was identified in 62/275 (22.5%). The remaining 5/275 (1.8%) CYP demonstrated no dystonia, spasticity or choreoathetosis.

Details of medication use are provided in Table 2. A total of 14 medications were identified across the cohort in use to reduce tone/abnormal movements. At the time of data collection, 98/275 (35.6%) CYP were receiving no medications for the management of abnormal tone/movement, 97/275 (35.3%) CYP 1 medication, 42/275 (15.3%) CYP 2 medications, 23/275

(8.4%) CYP 3 medications, 12/275 (4.4%) CYP 4 medications and 3/275 (1.1%) CYP 5 medications.

The most commonly used medications were baclofen (108/275, 39.3%), trihexyphenidyl (56/275, 20.4%), gabapentin (51/275, 18.5%), diazepam (36/275, 13.1%) and clonidine (28/275, 10.2%). Choice of medication appeared to differ depending upon whether clinically significant spasticity or dystonia was noted in the CYP (Figure 2). The use of baclofen did not seem to be significantly altered by the presence or absence of dystonia, but trihexyphenidyl, gabapentin and clonidine were all infrequently used when dystonia was not present (Figure 2(a)). Conversely, the presence of clinically significant spasticity seemed to increase the use of baclofen, but have minimal impact on the use of trihexyphenidyl, gabapentin or clonidine (Figure 2(b)). Diazepam use also did not seem to differ with the presence of clinically significant spasticity.

In addition to enteral medications for the management of abnormal tone/movements, 171/275 (62.2%) CYP were receiving botulinum toxin injections as part of their overall management.

An additional diagnosis of epilepsy had been made in 104/275 (37.4%) of CYP, with 68/104 (65.4%) receiving 1 Anti-Epileptic Drug (AED) and 27/104 (26.0%) 2 or more AEDs. A total of 16 different AEDs were identified, with the most commonly used being sodium valproate (51/275, 18.5%). In one case, the ketogenic diet was being used to manage epilepsy.

A total of 34/275 (12.4%) CYP had undergone a neurosurgical procedure – 3 DBS, 6 SDR, and 25 ITB.

Discussion

CP is a common condition, likely to be encountered frequently by professionals working across all settings in acute and community paediatrics. Despite this, at present a higher level of evidence exists to support the use of invasive neurosurgical interventions to manage tone, suitable for only a minority of CYP(9) compared to evidence for enteral medications, which are prescribed frequently for the majority of this patient group.

The data from this multi-centre prospective case review has demonstrated the complexity and variability of the motor phenotype, pharmacological management and associated co-morbidities of CYP with CP, illustrating the challenges in performing definitive trials of pharmacological intervention in this population. Data has been collected from tertiary care (specialist) clinics, and we believe is representative of practice in this setting in UK. Clinicians working in Paediatric tertiary care typically guide and advice the management of CYP by Secondary and Primary care teams (with active co-management of many CYP), and so our data is also likely to be applicable in these settings.

CYP with CP are commonly categorized on the basis of their predominant motor difficulty into “spastic”, “dyskinetic” or “ataxic” forms. This is an overly reductive approach, as in clinical practice a mixed picture is generally seen,

as underlined by our finding that 70.5% of CYP presented with dystonia and spasticity (+/- choreoathetosis). Isolated dystonia or spasticity was relatively infrequently seen. Ataxic cerebral palsy is very rare, and potentially over-reported(20). This is consistent with the findings of Rice and Colleagues, who identified frequent dystonia in a cohort of 129 CYP with “spastic” CP(7). If the results of future interventional studies are to be translatable into clinical practice, they must be undertaken in children with a representative picture of mixed tone/abnormal movements.

The HAT is a validated means of defining whether spasticity and/or dystonia are present in a child(18). No such tool exists for choreoathetosis, though the recently developed Dyskinesia Impairment Scale does provide a tool for the measurement of choreoathetosis separate from dystonia(21). The definitions of both chorea and athetosis proposed by the SCPE(22) are very similar to those proposed by the Taskforce on Childhood Movement Disorders(19), but challenges with the practical recognition of these movements have been raised(23). It is of note in our study the relatively infrequent recognition of choreoathetosis compared to dystonia, with 2/7 centres documenting no CYP with these abnormal movements over a calendar month. Further work is likely to be required prior to future multi-centre interventional studies to ensure the validity and reliability of the recognition of choreoathetosis between investigators.

Measuring the extent/severity of dystonia, spasticity and choreoathetosis in CYP is challenging, and generally relies upon the application of clinically

applied scales. A recent review of available scales for dystonia and choreoathetosis in children with Dyskinetic Cerebral Palsy identified significant limitations, not least of which was that they have been designed to classify movement disorders at the level of body function and structures, rather than activity or participation(24). Similarly, the measurement of spasticity in the clinical setting is challenging (25-27). Put simply, there is no "perfect" tool to measure these different motor abnormalities directly, and measuring a reduction of these symptoms in isolation would fail to capture the true impact of an intervention for CYP and their families and carers(28).

A wide range of medications were identified in the management of abnormal tone and movement in this cohort, with the presence of spasticity and dystonia appearing to separately influence the choice of medication. There is very limited data available regarding current clinical practice for prescribing of medications for the management of abnormal tone and movement in CP or in other childhood conditions. In a retrospective analysis of 278 CYP in the UK with dystonia of different aetiology, the most commonly used medications were baclofen, trihexyphenidyl, levodopa and diazepam(15). In a prospective study of the management of dystonia in 57 CYP with CP at a tertiary care centre in Australia, baclofen and gabapentin were the most commonly used oral medications(14). Baclofen is a Gamma-aminobutyric acid (GABA) B receptor agonist, and data from our presented study confirms its widespread use in the management of hypertonia in childhood. Despite this widespread use, evidence for its efficacy is extremely limited. Recent systematic reviews of oral pharmacological management of dystonia in CP found no studies of

baclofen meeting their inclusion criteria (9, 11). Evidence to support the use of oral baclofen (in contrast to intrathecal baclofen) in the management of spasticity is currently limited, with contradictory findings reported(13). Trihexyphenidyl, a centrally acting anti-cholinergic agent, has no role in the management of spasticity. A larger number of studies have examined the efficacy of trihexyphenidyl in the management of dystonia in CP, but results to date have been contradictory(9, 11). Whilst sufficient evidence was identified for the AAN guidelines to recommend the short-term use of diazepam (which potentiates the post-synaptic inhibitory effect of GABA) to reduce spasticity(13), longer term use for the management of spasticity and for reduction of dystonia is currently lacking(9, 11, 13). Gabapentin (an analogue of GABA) appears to be an increasingly used medication for tone reduction in CP, but published data is very limited. A retrospective study of gabapentin in 69 children with dystonia (Level 4 evidence), including 25 with CP reported perceived benefits(29). Similarly, the use of clonidine (a centrally acting alpha-adrenergic agonist) in the management of hypertonicity in childhood appears to becoming more common, but published data supporting this use is limited to isolated case reports, and a single retrospective study of 33 children with dystonia of varied aetiology (level 4 evidence)(11, 30). Gabapentin is a widely used medication for the management of neuropathic pain. It remains to be determined to what extent its use in CYP is focused primarily on reduction of pain, as opposed to a primary intention to reduce elevated tone and posturing (though these two aims are not entirely distinct). Given the limited efficacy of baclofen and trihexyphenydil experienced anecdotally in many CYP with high tone in CP, the growing use of gabapentin and clonidine is likely to reflect a

pragmatic approach by clinicians to exploring medications with established indications and safety profiles for new indications.

Further adding to the complexity of management in these CYP was the comorbid diagnosis of epilepsy in almost 40%, the use of botulinum toxin in 62.2%, and a previous neurosurgical intervention in 12.4%. Epilepsy is a common co-morbidity in CP, with data from the SCPE network from 1976-1998 reporting an overall incidence of 35% of CYP.(31). Higher rates of epilepsy were identified in CYP with dyskinetic or bilateral spastic CP. Many medications used primarily for the management of epilepsy may have a potentially beneficial effect on choreoathetoid movements (e.g. carbamazepine, levetiracetam)(11), posing further potential confounding factors for future definitive studies of interventions aimed at reducing abnormal tone and movements in this population. Additionally, the potential exists for AED medications to interact adversely with medications aimed at reducing tone and movement, in terms of drug metabolism and the risk of potentiating side effects (e.g. sedation/respiratory depression when baclofen and clobazam are used together).

A number of limitations must be acknowledged to our presented study. Firstly, motor phenotype was reported by each individual centre, with no measure of reliability or reproducibility of this assessment between centres. This is particularly pertinent given that 2/7 centres identified no choreoathetosis in the CYP reported. The determination of whether identified motor abnormalities were clinically significant was subjective, and, as such, subject to the biases

of the individual clinicians. Data was collected on current medication use, but no data was recorded on doses (units/kg), perceived or measured efficacy, side effects, or previous medication use. No data was collected on the clinical reasoning guiding medication choices for the CYP reviewed. Additionally, data was not collected around therapeutic interventions, orthoses, and broader non-neurological medical co-morbidities.

Conclusion:

This study highlights that CYP with CP represent a complex patient group, with a typically mixed-motor phenotype, and often multi-modal methods of management of abnormal tone and movements. A large number of medications are in current use for the management of these motor difficulties, most commonly baclofen and trihexyphenidyl. Currently, only very limited evidence is available to support the efficacy of these medications,

There is a pressing need for definitive studies to guide clinical practice, but intelligent and pragmatic trial design is required. Trial design must also accommodate co-morbid epilepsy, in addition to wider medical co-morbidities. It must consider confounding interventions, including therapeutic and non-pharmacological treatments. There must be multi-stakeholder engagement, to include CYP, Parents, allied health professionals, medical and surgical clinicians. A priority list is required to enable a collaborative approach which will enable the clinical research community to move forward as a whole to address this function, addressing outcomes across different levels of function, across all domains of the ICF (some provisional suggestions for which are outlined in Box 2). It is imperative that the design of future trials encompasses

these complexities to allow their outputs to directly inform clinical practice, and lead to tangible improvements in quality of life for CYP with CP.

Contributorship Statement

DEL conceptualised and designed the study, and wrote the initial manuscript draft, BC and AB contributed to study design, and contributed to data collection, SA, AD, TDA, RK, RL, CL, SM and MS contributed to data collection and analysis, JC contributed to study design, data collection and analysis. All authors reviewed and revised the manuscript, and approved the final version as submitted.

What is already known on this topic:

3 – 25 words each

Cerebral palsy is the most common diagnosis in children who present with hypertonia; they present with a mixed pattern of tone and movement abnormalities.

Despite widespread use of medications for tone management, there is little evidence to inform best practice in pharmacological management of hypertonia in this population.

Research design is limited by the complexity of presentation: the definition of the population, confounding co-morbidities interventions and lack of robust outcome measures.

What this paper adds:

2 – 25 words each

This paper reports the described motor phenotype of CYP with CP presenting to specialist neurodisability services in the UK.

It is the first paper to report current prescribing practice for this population, and highlights the multiple medications used for tone management.

It highlights the prevalence of epilepsy as a co-morbidity, with anti-convulsant medication prescription, and confounding medical and surgical interventions which may affect tone management.

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Tables:

GMFCS	Level	Number	% Cohort
	I	35	12.7
	II	51	18.5
	III	24	8.7
	IV	70	25.5
	V	95	34.5
MACS	I	37	13.5
	II	70	25.4
	III	32	11.6
	IV	48	17.5
	V	71	25.8
Dystonia	None	53	19.3
	Not Significant	50	18.2
	Clinically Significant	172	62.5
Spasticity	None	33	12.0
	Not Significant	66	24.0
	Clinically Significant	176	64.0
Choreoathetosis	None	200	72.7
	Not Significant	49	17.8
	Clinically Significant	26	9.5
Epilepsy	Yes	104	37.8
	No	171	62.2
Botulinum Toxin Program	Yes	171	62.2
	No	104	37.8
Deep Brain Stimulation	Yes	3	1.1
	No	272	98.9
Intrathecal Baclofen	Yes	25	9.1
	No	250	90.9
Selective Dorsal Rhizotomy	Yes	6	3.2
	No	269	97.8

Table 1: Clinical Features of CYP with CP reviewed in clinic.

Abbreviations used: “GMFCS” – Gross Motor Classification System, “MACS” – Manual Ability Classification System.

Medications Type	Medication	Number	% Overall cohort
Tone/Movement	Baclofen	108	39.3
	Trihexyphenidyl	56	20.4
	Gabapentin	51	18.5
	Diazepam	36	13.1
	Clonidine	28	10.2
	Chloral Hydrate	11	4.0
	Levodopa	9	3.3
	Nitrazepam	2	0.7
	Clonazepam	2	0.7
	Midazolam	1	0.4
	Risperidone	1	0.4
	Nabiximol	1	0.4
	Amitriptyline	1	0.4
	Tizanidine	1	0.4
Epilepsy	Sodium Valproate	51	18.5
	Levetiracetam	23	8.4
	Carbamazepine	19	6.9
	Lamotrigine	11	4.1
	Topiramate	10	3.6
	Clobazam	3	1.1
	Nitrazepam	2	0.7
	Oxcarbazepine	2	0.7
	Lacosamide	2	0.7
	Vigabatrin	1	0.4
	Clonazepam	1	0.4
	Phenytoin	1	0.4
	Phenobarbitone	1	0.4

	Zonisamide	1	0.4
	Calcium Folinate	1	0.4
	Perampanel	1	0.4

Table 2: Medication Use across the cohort.

Figure Legends

Figure 1:

1(a) Distribution of Gross Motor Function Classification System (GMFCS) and Manual Ability Classification System (MACS) levels across the cohort.1(b) Motor phenotype of CYP in the cohort, with presence of spasticity and/dystonia defined as per the Hypertonia Assessment Tool (HAT) and choreoathetosis as defined by the Taskforce on Childhood Motor disorders. Clinical significance of these features was based on judgment of the reporting clinicians.

Figure 2:

Frequency of individual medication use depending upon whether CYP demonstrated clinically significant (a) Dystonia, (b) Spasticity or (c) Choreoathetosis.

Box 1

Spasticity	Features denoting presence of spasticity according to Hypertonia Assessment Tool(10) • Velocity - dependent resistance to stretch • Presence of spastic catch
Dystonia	Features denoting presence of dystonia according to Hypertonia Assessment Tool (10) • Increased involuntary movements or postures of the designated limb with tactile stimulus of a distant body part • Increased involuntary movements or postures with purposeful movement of a distant body part • Increased tone with movement of a distant body part
Choreoathetosis	As defined by the Taskforce on Childhood Movement Disorders (19) Chorea is an ongoing random-appearing sequence of one or more discrete involuntary movements or movement fragments. Athetosis is a slow, continuous, involuntary writhing movement that prevents maintenance of a stable posture

Box 2

Priorities to be addressed for development of future trial design of medications for the treatment of tone and movement in CP
• How to standardize a description of the motor profile of children with CP? • How to ensure the reliability of motor phenotyping across multiple centres and clinicians?

- Accepting a single trial cannot include all children and young people with CP. How should this heterogenous cohort be divided into biologically and clinically meaningful studies for future trial designs (e.g by functional level, age, aetiology, features of motor phenotype)?
- What Outcome measures should be used? Measures must map across all domains of the ICF, and be meaningful to children and young people with CP, their parents/carers and clinicians alike?
- Over what time scale should studies be performed?
- What medications should be trialed, and compared to what? Would a placebo arm be acceptable to children and young people with CP, their parents/carers and clinicians alike? What medication would be considered the “standard of care”?
- Given the off license use of most medications in current clinical practice, what dosing range and schedules should be used for medications included in future pharmacological studies?
- To what extent can other aspects of care be standardized during the time children and young people with CP are enrolled in future studies (e.g. application of orthoses)?
- Should future trials focus on medication naïve children and young people? This would simplify study design, but would limit recruitment, preventing many children and young people with CP benefitting from and contributing to trial enrollment.

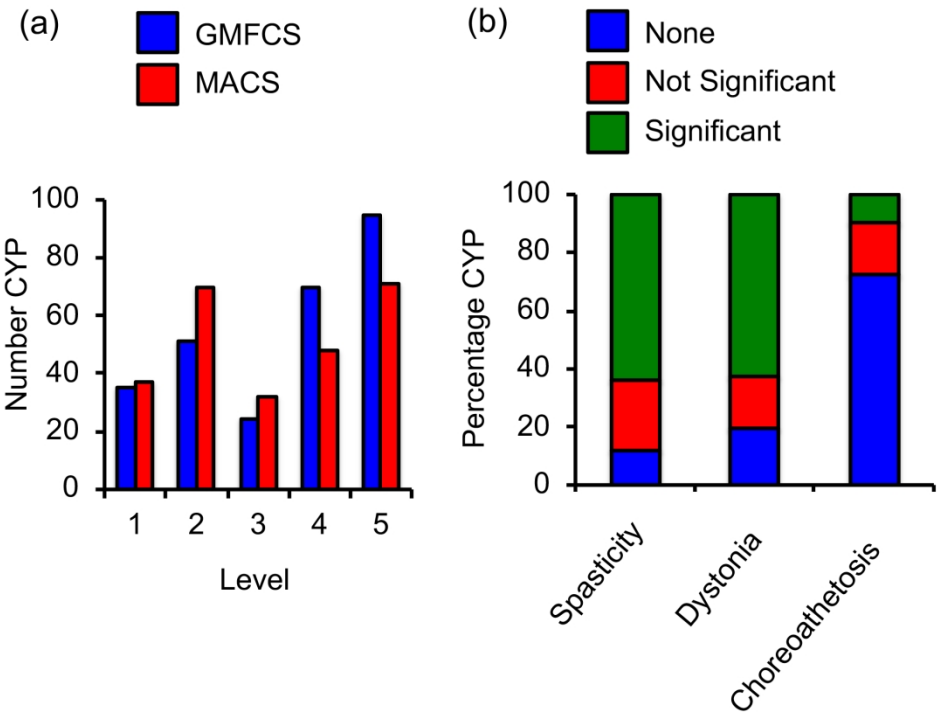

Figure 1

Figure 1:
1(a) Distribution of Gross Motor Function Classification System (GMFCS) and Manual Ability Classification System (MACS) levels across the cohort.1(b) Motor phenotype of CYP in the cohort, with presence of spasticity and/dystonia defined as per the Hypertonia Assessment Tool (HAT) and choreoathetosis as defined by the Taskforce on Childhood Motor disorders. Clinical significance of these features was based on judgment of the reporting clinicians.

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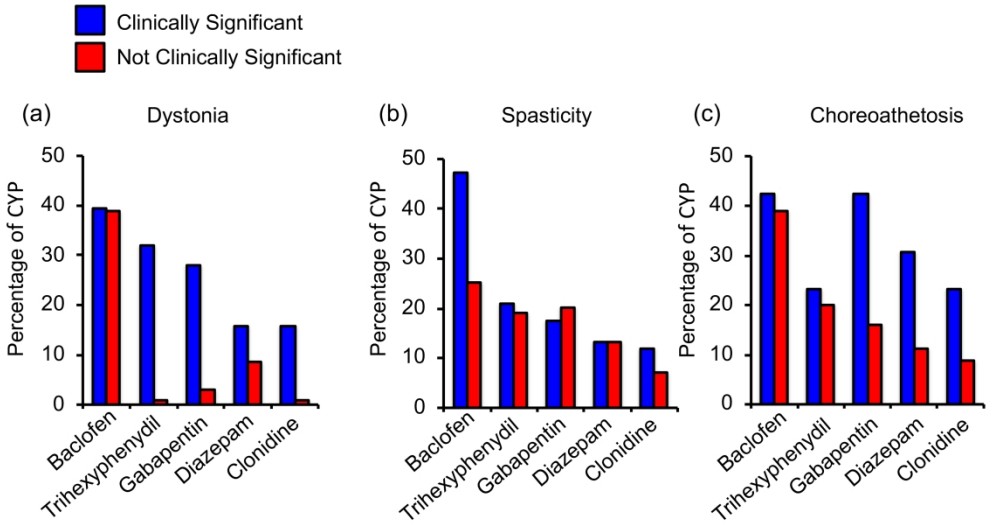

Figure 2:
Frequency of individual medication use depending upon whether CYP demonstrated clinically significant (a) Dystonia, (b) Spasticity or (c) Choreoathetosis.

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